

**NOT FOR PUBLICATION**

**UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

MERCK SHARP & DOHME CORP.,

Plaintiff,

v.

SANDOZ INC.,

Defendant.

Case No. 3:12-cv-03289-PGS-LHG

**MEMORANDUM OPINION**

SHERIDAN, District Judge.

**I. INTRODUCTION**

This matter is before the Court on Defendant, Sandoz, Inc.’s (“Sandoz”) counterclaim against Plaintiff, Merck Sharp & Dohme Corp. (“Merck”) as to the invalidity of claims 15, 16, 18 and 19 (the “Asserted Claims”) in U.S. Patent No. 5,691,336 (“the ’336 patent”) for obviousness. The ’336 patent was issued to Merck on November 25, 1997, claiming the new chemical compound known today as fosaprepitant dimeglumine, commercially known as EMEND® for Injection. The claimed compound is utilized to prevent chemotherapy induced nausea and vomiting (“CINV”), a side effect of highly emetogenic chemotherapy administered for the treatment of certain forms of cancer. Fosaprepitant dimeglumine is able to obstruct a neurological pathway known as the Substance P-NK-1 receptor system, and is administered in intravenous form to patients. (Tr. 395:25-399:20.)

A bench trial was held in this matter on March 3, 4, 6, 9, 10, and 30, 2015, with closing arguments on May 5, 2015. During that trial, the Court acted as the trier of fact, and it adopted the

standards which are ordinarily utilized by a jury to evaluate the credibility and weight of the evidence. *See* Model Jury Charges of the Third Circuit, §§ 1.5, 1.6, and 1.7.

## **II. LEGAL STANDARD**

Because this case centers around Sandoz's claim of obviousness, and Merck's corresponding asserted defense of non-obviousness, of the '336 patent, the burden of proof in this matter rests on Sandoz. Patents are presumed to be valid upon issuance, and obviousness of a patent's claims must be proved by clear and convincing evidence. *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356 (Fed. Cir. 2008). A determination of obviousness under 35 U.S.C. § 103(a) is a legal question that finds its basis in underlying factual determinations. *Eisai Co. Ltd.*, 533 F.3d at 1356; *see also Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1007 (Fed. Cir. 2009). The appropriate factual inquiry in determining obviousness turns on the four *Graham* factors: "1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness." *Eisai Co. Ltd.*, 533 F.3d at 1356 (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)).

Where the patent in dispute claims a chemical compound, "the analysis of the third *Graham* factor (the differences between the claimed invention and the prior art) often turns on the structural similarities and differences between the claimed compound and the prior art compounds." *Eisai Co. Ltd.*, 533 F.3d at 1356-57; *see also Altana Pharma AG*, 566 F.3d at 1007. In cases where the obviousness argument is based upon the structural similarity between the claimed compound and prior art compounds, obviousness may "be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound." *Eisai*, 533 F.3d at 1357. "The

reason or motivation need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship . . . to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old.” *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (alteration issues) (internal quotation marks and citations omitted).

### **III. FINDINGS OF FACT**

In light of the testimony, including the credibility of witnesses and the evidence of proof, the Court finds the following facts:

#### **A. Background**

1. Merck is the assignee of the '336 patent, is entitled “Morpholine Compounds are Prodrugs Useful as Tachykinin Receptor Antagonists” and was issued by the United States Patent and Trademark Office (“PTO”) on November 25, 1997. (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 5, ¶ 9.) The '336 patent issued from U.S. Application No. 08/525,870 (“the '870 application”), filed on September 8, 1995. (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 5, ¶ 11.)

2. The '336 patent claims priority to U.S. Application No. 08/206,771 (“the '771 application”), filed on March 4, 1994, and to International Application No. PCT/US95/02551 (“PCT '551”), filed on February 28, 1995. (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 5, ¶ 12.)

3. The '336 patent contains certain claims that are directed to the new chemical compound known today as fosaprepitant dimeglumine. (Tr. at 96:2-21; PTX-001.0081-82.) More specifically, the Asserted Claims at trial were Claims 15, 16, 18, and 19 of the '336 patent, each

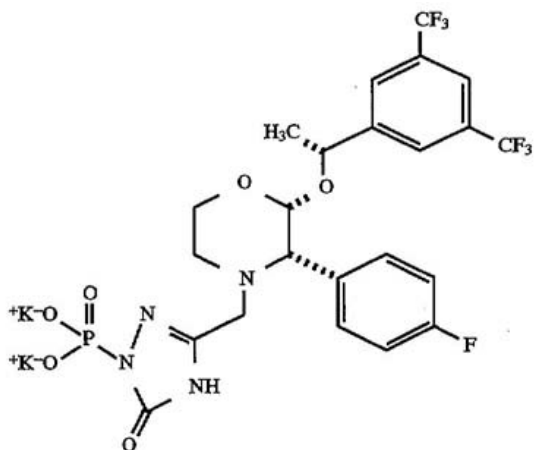
of which specifically claims by formal chemical name or chemical structure the compound that was later named fosaprepitant dimeglumine. (Tr. at 96:7-97:1, 424:12-18, 426:15-20.)

4. The chemical compound fosaprepitant dimeglumine is disclosed and specifically claimed in the '336 patent, which is the patent-in-suit for trial in this litigation. (Tr. at 96:2-21.)

5. Claim 15 of the '336 patent states: "The compound of claim 14 wherein the pharmaceutically acceptable salt is the bis(N-methyl-D-glucamine) salt." In turn, Claim 14 of the '336 patent states: "A compound which is: 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine; or a pharmaceutically acceptable salt thereof." (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 5, ¶ 13.)

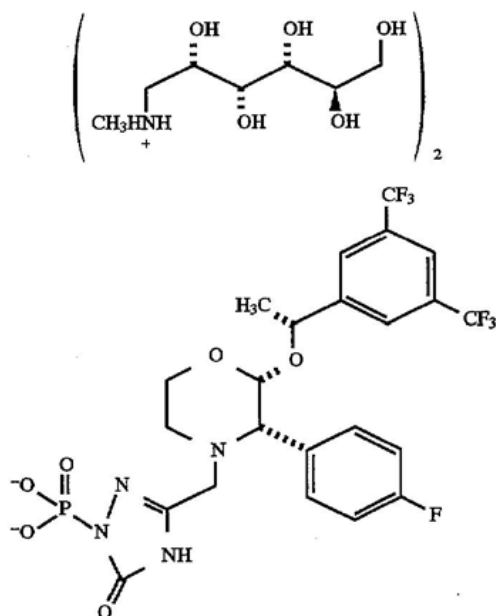
6. Claim 16 of the '336 patent states: "A compound which is 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluoro)phenyl-4-(3-(1-phosphoryl-5-oxo-4H-1,2,4-triazolo)methylmorpholine, bis(N-methyl-D-glucamine)." (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 6, ¶ 14.)

7. Claim 18 of the '336 patent states: "The compound of claim 17 wherein K<sup>+</sup> is N-methyl-D-glucamine." In turn, Claim 17 of the '336 patent states: "A compound which is:



wherein K<sup>+</sup> is a pharmaceutically acceptable counterion.” (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 6, ¶ 15.)

8. Claim 19 of the '336 patent states: “A compound which is:



(ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 6, ¶ 16.)

9. On January 24, 2012, Sandoz submitted to the United States Food and Drug Administration (“FDA”) Abbreviated New Drug Application (“ANDA”) No. 203939 seeking approval to manufacture, use, and sell fosaprepitant dimeglumine IV powder, Eq 150 mg base/vial (“Sandoz ANDA Product”) prior to the expiration of the '336 patent. (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 6, ¶ 17.)

10. Sandoz’s ANDA included a certification pursuant to 21 U.S.C. § 355(j)(2)(A)(vii)(IV) of the Federal Food, Drug, and Cosmetic Act (“Paragraph IV Certification”) alleging that all claims of the '336 patent were invalid, unenforceable, and/or would not be infringed by the manufacture, use, importation, sale, or offer for sale of the Sandoz ANDA Product. (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 7, ¶ 18.)

11. Sandoz sent a letter dated April 23, 2012 (“the Sandoz Notice Letter”) to Merck, which was delivered thereafter, in which Sandoz represented that it had filed an ANDA for the Sandoz ANDA product, that its ANDA contains a certification with respect to the ’336 patent, and that it seeks approval of its ANDA prior to the expiration of the ’336 patent. (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 7, ¶ 19.)

12. The Sandoz Notice Letter contained an assertion with respect to the Asserted Claims of the ’336 patent that those claims are invalid for obviousness under 35 U.S.C. § 103. (Tr. at 169:7-13.). The instant action was commenced within 45 days of the Sandoz Notice Letter. (ECF NO. 1, Complaint.). As a result, the FDA has automatically stayed final approval of Sandoz’s ANDA. The FDA’s automatic stay expired on Monday, July 27, 2015.<sup>1</sup> (ECF NO. 139, January 16, 2014 Letter, at 2.) The parties agreed to extend the stay to August 22, 2015. (ECF No. 280).

13. Merck has asserted that, by submitting to the FDA Sandoz’s ANDA No. 203939 seeking approval to manufacture, use, and sell the Sandoz ANDA Product prior to the expiration of the ’336 patent, Sandoz infringes the Asserted Claims of the ’336 patent (“the Asserted Claims”). (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 7, ¶ 20.)

14. The parties have stipulated that the Fosaprepitant Dimeglumine IV Powder, Eq 150 mg base/vial described in Sandoz’s ANDA No. 203939 (“Sandoz’s ANDA Product”) is literally within the scope of the Asserted Claims of the ’336 patent and would infringe the Asserted Claims of the ’336 patent upon commercialization in the U.S., provided that the Asserted Claims are not proven invalid. (ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 7, ¶ 21.)

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<sup>1</sup> The parties dispute the actual date of the expiration of the 30 month stay. Sandoz asserts that the stay ended on Saturday, July 25, 2015. Merck asserts that the stay ended on Monday, July 27, 2015.

15. In view of the parties' stipulation on infringement, the sole issue tried in this action was whether, under 35 U.S.C. § 103, Sandoz proved by clear and convincing evidence that each of the Asserted Claims would have been obvious to a POSA as of the time of their invention. (Tr. at 56:4-9; ECF NO. 232, Joint Final Pretrial Order, Stipulation of Facts, at 7, ¶ 21.)

16. The parties agree that the relevant "time of the invention" for the Asserted Claims in this case is 1994. Fosaprepitant dimeglumine was synthesized by April 29, 1994. (Tr. at 424:23-435:9; PTX-187.0072.) By September 1, 1994, the Merck scientists had submitted a report to the Merck Research Management Committee ("RMC") detailing the Merck scientists' testing of fosaprepitant dimeglumine to demonstrate its ability to provide the desired therapeutic activity by functioning as a prodrug that remained a stable compound prior to administration, but then would be enzymatically converted in the body to a form that would bind to NK-1 receptors. (Tr. at 428:2-9, 429:24-430:9, 432:14-22, 433:1-19; PTX-184.0002-3.).

#### **B. Witnesses**

17. At trial, Dr. David H. Sherman was presented by Sandoz as an expert in support of its *prima facie* obviousness case. Dr. Sherman is the Hans Vahlteich Professor of Medicinal Chemistry at the University of Michigan and also holds the positions of Professor in the Department of Microbiology and Immunology in University of Michigan's medical school, Founding Director of the Center for Chemical Genomics, and member of the Executive Advisory Board of the University of Michigan's academic drug discovery operation. (Tr. at 86:8-20.). Dr. Sherman received his Bachelor of Arts degree from the University of California Santa Cruz and his Ph.D. from Columbia University before doing post-doctoral fellowships at Yale Medical School and the Massachusetts Institute of Technology and then taking jobs at a biotechnology

company in Cambridge, Massachusetts and a research institute in the United Kingdom. (Tr. at 85:1-25.)

18. Dr. Sherman testified that he received from counsel the documents that he considered relevant to his obviousness opinions, including certain confidential Merck research documents, and what he reviewed he considered to be a complete set of information to him to “understand and make” his opinions. (Tr. at 160:2-13, 161:14-24.)

19. At trial, Dr. William R. Roush testified as an expert on Merck’s behalf. Dr. Roush is employed at Scripps Research Institute in Jupiter, Florida as a Professor of Chemistry, the Executive Director of Medicinal Chemistry of a drug discovery program internal to the Scripps Research Institute, and the Associate Dean of the Scripps Research Institute Ph.D. program. (Tr. at 419:11-18.) Dr. Roush received his Bachelor’s Degree from the University of California Los Angeles in 1974 and his Ph.D. in Chemistry from Harvard University in 1977 before spending a year conducting post-doctoral research at Harvard. He began his academic career as a faculty member in 1978 at the Massachusetts Institute of Technology. (Tr. at 420:13-25.) Dr. Roush has held faculty positions at four institutions: the Massachusetts Institute of Technology, Indiana University, the University of Michigan in Ann Arbor, and at Scripps Research Institute in Florida. (Tr. at 420:23-421:2.)

20. Dr. Roush was retained as an expert for Merck in July 2012. (Tr. at 439:10-11.) He conducted a literature search and read background documents with which he familiarized himself with the art of NK-1 receptor antagonists as of 1994 – which was a significant body of information. (Tr. at 439:12-19.) In addition to Dr. Roush, several fact witnesses testified concerning Merck’s extensive, internal and confidential NK-1 receptor antagonist research work in the early 1990s.

21. Jeffrey Hale, Ph.D. is a named inventor on the '336 patent, and testified live at trial. (PTX-001.0001.) Dr. Hale began his career at Merck as an intern in the summer of 1984 and started as a full-time employee in July of 1985 after receiving his Bachelor of Science in chemistry from Stevens Institute of Technology in May of 1985. (Tr. at 618:7-17.) When Dr. Hale joined Merck in 1985, his supervisor was Dr. Conrad Dorn, who at that time had been with Merck for more than two decades. Dr. Dorn taught Dr. Hale the art of synthetic chemistry in the context of drug discovery, how to handle compounds, how to purify them, and how to work iteratively to develop new compounds. (Tr. at 620:2-18.) Upon starting his career at Merck, Dr. Hale intended to pursue graduate studies and began taking night classes at Rutgers University to further that goal. Merck allowed Dr. Hale to take a two year paid leave of absence to complete his research work, after which he returned to Merck in 1992 and received his Ph.D. that same year. (Tr. at 619:7-24.)

22. When Dr. Hale returned to Merck in 1992, he joined Merck's "Substance P program," in which Merck scientists were investigating new chemical compounds with activity as NK-1 receptor antagonists, and their potential use in the treatment of several disorders, including pain and emesis. (Tr. at 624:4-12.)

23. Malcolm MacCoss, Ph.D. is a named inventor on the '336 patent. Portions of his deposition were presented at trial. (PTX-001.0001.) Malcolm MacCoss received an Honors Degree in chemistry and a Ph.D. in chemistry from the University of Birmingham, United Kingdom in 1968 and 1971, respectively. (Tr. at 219:18-220:9, 224:3-6.) Following his Ph.D., Dr. MacCoss became a post-doctoral fellow and later a research associate at the University of Alberta, Canada until he left in 1976. (Tr. at 224:14-22.) From 1976 to 1982, Dr. MacCoss worked at Argonne National Laboratory. (Tr. at 226:9-13.) Dr. MacCoss was awarded the University of Chicago Medal for Distinguished Performance at Argonne National Laboratory for his work on

novel phospholipid-nucleoside conjugates as prodrugs for anticancer agents. (Tr. at 327:4-11.) In 1982, Malcolm MacCoss joined Merck & Company, and from 1991 to 1993 held the title of Director of Medicinal Chemical Research for the Substance P project. (Tr. at 226:20-24, 269:10-20.) In the mid-1980s, while working at Merck, Dr. MacCoss had involvement with a project designing a complex prodrug nucleoside analog. (Tr. at 244:10-245:5.)

24. Sander Mills, Ph.D. is a named inventor on the '336 patent. (PTX- 001.0001.) Portions of his deposition were presented at trial. Dr. Mills received his Bachelor of Arts degree in chemistry from Drew University in 1978 and received his Ph.D. from the University of Illinois in Urbana-Champaign in 1983. (Tr. at 795:18-796:17.) After receiving his Ph.D., Dr. Mills joined the University of California at Berkeley as a post-doctoral fellow, staying there for approximately two years. (Tr. at 797:3-13.). Dr. Mills subsequently joined the process chemistry group at Merck. In 1989, however, he moved to Merck's medicinal chemistry group, where he worked on elastase compounds before working on the Substance P program. (Tr. at 621:22-622:2.) In the 1992-1994 timeframe while working on the Substance P program, Dr. Mills acted as scientific supervisor to Dr. Hale. (Tr. at 645:21- 646:11.)

25. Dr. Mills's background and training in process chemistry was unusual for a medicinal chemist to have in the context of new drug discovery. Dr. Mills' skills as a process chemist allowed him to be, as Dr. Hale described, "really good in the lab, he could identify fruitful ways for optimizing chemical reactions." (Tr. at 622:4-17.) As Dr. Hale testified, there are differences between medicinal chemistry and process chemistry. He stated that "in a broad sense medicinal chemistry is a chemistry to try to identify compounds that you would hope would be a drug," whereas "process chemists are responsible for taking laboratory scale syntheses of a drug

and converting that so that Merck could eventually produce this drug on a very large scale.” (Tr. at 622:18-25.)

26. Conrad Dorn, Ph.D. is a named inventor on the '336 patent. Portions of his deposition by written questions and answers were presented at trial. (PTX-001.0001.) Dr. Dorn had joined Merck by the 1970s, and he acted as supervisor to Dr. Hale when Dr. Hale joined Merck in 1985. (Tr. at 620:2-6.) Dr. Dorn was a member of the chemistry group that worked on the Substance P program. (Tr. at 270:2-5.) Dr. Dorn was a pharmaceutical chemist by training but worked at Merck as a medicinal chemist. Dr. Hale described pharmaceutical chemistry as knowing how to make drugs work as opposed to how to make active substances. Throughout Dr. Dorn's career, he developed significant experience in medicinal chemistry. (Tr. at 620:5-11.)

27. Dr. Hale described at trial how Dr. Dorn had mentored him, teaching Dr. Hale “how to do synthetic chemistry in the context of drug discovery, how to handle compounds, purify them, [and] how to iteratively do data on work to new compounds.” (Tr. at 620:12-18.)

28. In 1993-1994, the timeframe leading up to the invention of fosaprepitant dimeglumine, Dr. Dorn was a senior member of the Substance P program and had previous experience in salvaging potential candidates via salt formation. (Tr. at 790:17-18, 793:25-794:2.)

29. Paul Finke, Ph.D. is not a named inventor on the '336 patent, but was a member of the Substance P group in 1993-1994, the timeframe leading up to the invention of fosaprepitant dimeglumine. Portions of his deposition were presented at trial. Dr. Finke was a member of the chemistry synthetic group and made many analogs during his work on the substance P program. (Tr. at 281:25-282:2.)

31. Shrenik Shah, Ph.D. is not a named inventor on the '336 patent, but was a member of the Substance P group in 1993-1994, the timeframe leading up to the invention of fosaprepitant

dimeglumine. Portions of his depositions were presented at trial. Dr. Shah was a medicinal chemist working for Dr. MacCoss as a member of the Substance P project. (Tr. at 317:5-11.)

32. Dr. Rogers is an Advanced Practice Registered Nurse (“APRN”) specializing in cancer care with almost 35 years of experience. (Tr. at 387:13-25.) An APRN is a nurse who has been prepared at the graduate level to provide advanced health care to a group of specialty patients such as cancer patients. (*Id.*) APRNs specializing in cancer care provide advanced supportive care to cancer patients including the management of CINV, which is one of the biggest issues in supportive cancer care. (Tr. at 388:4-14.) Dr. Rogers has a Baccalaureate of Science in Nursing from East Tennessee State University, a Masters in Nursing from Emory University, and a Doctorate in Adult Education with a focus in advanced continuing education for professionals from North Carolina State University. (Tr. at 389:2-16; PTX-109.0007-8.) During the course of managing cancer patients, Dr. Rogers has been involved in both prescribing and administering antiemetic drugs for the prevention of CINV, as well as preparing other oncology nurses in administering these drugs. (Tr. at 388:15-24.) Dr. Rogers has managed thousands of cancer patients over the course of her career. (Tr. at 390:7-16.)

33. Dr. Rogers offered opinions regarding the importance of EMEND® for Injection (fosaprepitant dimeglumine) in the prevention of acute and delayed CINV caused by highly emetogenic chemotherapy (“HEC”), and its advantage over EMEND® Oral, which was the only other FDA-approved NK-1 receptor antagonist available as of the launch of the 150 mg single-dose EMEND® for Injection.

34. Mr. Raymond Sims offered opinions regarding the commercial success of EMEND® for Injection. Mr. Sims is employed at Charles River Associates in Chicago as a vice-president in the intellectual property practice. (Tr. at 578:5-8; PTX-111.) Mr. Sims has a Bachelor

of Commerce degree with concentrations in accounting and financing from the University of Calgary, and a Master of Management from the Kellogg Graduate School of Management at Northwestern University. (Tr. at 578:24-579:5; PTX-111.) Mr. Sims is an expert in intellectual property research and analysis regarding whether the patented product is a commercial success. (Tr. at 579:9-15.)

35. Merck also presented the depositions testimony of Dr. Indranil Nandi, Sandoz's Rule 30(b)(6) witness. Dr. Nandi was Executive Director, Portfolio and Project Management at Sandoz. (Tr. at 821:7-9.) Dr. Nandi testified for Sandoz regarding its evaluation of the anticipated profitability of fosaprepitant dimeglumine.

36. Ms. Catharine Lawton was Sandoz's expert on objective indicia of nonobviousness, opining on commercial success. Ms. Lawton is a managing director at Berkley Research Group. (Tr. at 860:12-13.) Ms. Lawton has a Bachelor of Science degree in finance with minors in economics and political science from the University of Illinois in Urbana-Champaign. (Tr. at 861:24-862:4.) Ms. Lawton's experience relates to financial and economic issues and she does not have any specialized knowledge about the care of cancer patients and the prevention of CINV. (Tr. at 907:12-19; DTX-123.0002.)

37. Ms. Lawton had relied on Sandoz's expert Dr. Gary Morrow for her understanding about the patented technology and the way EMEND® for Injection worked in forming her opinions on commercial success and preparing her expert report. (Tr. at 908:25-909:8.) According to Sandoz, Dr. Morrow specialized in side-effect management of cancer control and is an expert in the field of CINV. (D.I. 232, Joint Final Pretrial Order, Expert Witnesses, at 254.) Sandoz disclosed in the final pretrial order that it intended to call Dr. Morrow as a witness at trial. (D.I. 232, Joint Final Pretrial Order, Expert Witnesses, at 256.) Dr. Morrow was scheduled to present his testimony

at trial on March 30, 2015. (D.I. 203.) However, on March 25, 2015, Sandoz informed the Court and Merck that Sandoz no longer intended to call Dr. Morrow to testify at trial. (D.I. 245.)

38. Ms. Lawton testified that she does not have the background to say why a medical professional would prescribe a particular medication for CINV. (Tr. at 908:21-24.)

### **C. Credibility of Witnesses**

39. Most of the witnesses at trial seemed generally credible. However, one witness in particular came to conclusions that were less than credible: Dr. Sherman. At trial, Dr. Sherman's testimony was not focused on the state of mind of the POSA in 1994, who lacked the benefit of Merck's confidential research or hindsight information available after 1994.

40. Dr. Sherman testified that he has never worked personally with a compound that acts as an antagonist of an NK-1 receptor, nor has he ever designed an improved NK-1 receptor antagonist compound. (Tr. at 142:4-13.) Dr. Sherman also testified that he has never designed a compound that received FDA approval as an active ingredient in a pharmaceutical product – though he stated that he is presently working toward that goal after a career spanning over 30 years. (Tr. at 207:17-23; DTX-131.0001-2.)

41. In his expert report on alleged obviousness in this case, Dr. Sherman relied on FDA product information about Merck's oral EMEND® (aprepitant) and EMEND® for Injection (fosaprepitant dimeglumine) products; presentations given after the time of invention by Merck scientists; publications dated after the time of invention; confidential Merck research documents; non-prior art deposition exhibits; and Sandoz's October 16, 2012 contentions. None of these sources are prior art to the '336 patent. (Tr. at 147:21-148:3, 148:8-18, 148:19-149:3, 149:7- 15, 151:22-152:5.) Dr. Sherman admitted that his expert report, as originally submitted in this case, relied upon prior art references that he first looked for in July 2013 notwithstanding his retention

in January 2013, and that, after those references were stricken from the case, he subscribed to the report and an opinion of obviousness without using those additional references. (Tr. at 143:19-144:8.)

42. Of the remaining references relied upon by Dr. Sherman in his expert report, he admitted on cross-examination that he specifically considered the following non-prior art documents in forming his opinions in this case: FDA product information from 2003, 2005, 2006, and 2008 about Merck's EMEND® and EMEND® for Injection products; PowerPoint presentations from Merck's scientists in 2004 to 2010; 25 publications spanning from 1995 to 2011; 45 internal and confidential Merck research documents; over 70 non-prior art exhibits from depositions of Merck witnesses; and Sandoz's October 16, 2012 contentions that the '336 patent was invalid. (Tr. at 147:1-11, 147:21-149:15, 151:22-152:5.)

43. Upon further cross-examination, Dr. Sherman admitted that the expressed bases for his opinion in his expert report included the FDA approval of EMEND® on March 27, 2003, though he tried to describe it as only "background" material after conceding it was not prior art. (Tr. at 154:4-8, 155:11-14; PTX362.0008.) The bases for Dr. Sherman's opinion also included the 2003 product insert and label for EMEND® as well as Merck's marketing of EMEND® after FDA approval in 2003, both of which he also tried to describe as "background" material. (Tr. at 154:9-20, 155:15-20; PTX362.0008.) Dr. Sherman also admitted that one of the bases for his opinion in his expert report was the January 25, 2008 FDA approval of EMEND® for Injection, which is not prior art. (Tr. at 154:21-23, 155:21-24; PTX362.0010.) Another basis for Dr. Sherman's opinion, admitted during cross-examination, was the 2008 EMEND® for Injection product insert, which is not prior art. (Tr. at 154:24-155:6, 155:25-156:2; PTX362.0008.)

44. Even though he admitted that the 2008 EMEND® for Injection product insert was not prior art, Sandoz elicited testimony from Dr. Sherman on direct examination during Dr. Sherman's explanation of his opinion of obviousness, specifically relying on this document. (E.g., 94:14-20, 95:22-96:1.)

45. Virtually every document cited in the section of Dr. Sherman's expert report entitled "BASES FOR OPINIONS AND MATERIALS CONSIDERED" was in fact not prior art. (Tr. at 155:11-156:2; PTX362.0008-11.)

46. In his direct testimony concerning alleged obviousness, Dr. Sherman again relied on the 2008 EMEND® for Injection label to explain the conversion of fosaprepitant to "aprepitant," (Tr. at 148:4-7, 154:24-155:6), which he admitted is not information that could have been considered by a hypothetical artisan at a time just before the invention and it was not prior art. (Tr. at 166:2-8.)

47. Dr. Sherman did not offer any testimony at trial that a POSA would have understood the conversion of fosaprepitant to "aprepitant" without the use of the 2008 EMEND® for Injection label at a time that was prior to the invention of the '336 patent.

48. In forming his opinions, Dr. Sherman did not feel it was necessary to look to whether Sandoz itself had a body of literature on information about what was actually ongoing in the NK-1 literature at the time of invention in light of, according to Dr. Sherman, "the relevant patents and what was there and what they were referencing." (Tr. at 179:17-23; DTX-016.0040-93.)

49. The Court finds that Dr. Sherman's ultimate conclusions as to the necessity of a lead compound analysis, as well as which compound would have been a lead compound, were suspect. These conclusions were therefore afforded little weight by the Court.

#### **D. The Development Of The Claimed Compound**

50. NK-1 receptor antagonist compounds are molecules that act to block the activity of the NK-1 receptor, and development of these molecules started at the beginning of the 1980s. (PTX-321.0002.) NK-1 receptor antagonist compounds were thought in the 1980s – and up to the 1994 time period – to have many potential therapeutic applications. (Tr. at 441:18-443:15; PTX-321.0038-44.)

51. The first generation of NK-1 receptor antagonist compounds were based on peptide molecules, and were developed and characterized in the 1980s and early 1990s. These compounds, however, suffered from issues such as low potency, poor bioselectivity, and other off-target activities. (PTX-321.0012; see also Tr. at 440:1-5.)

52. The next generation of NK-1 receptor antagonist compounds began with the introduction of a Pfizer compound known as CP 96,345, which was the first published non-peptide NK-1 receptor antagonist compound having high potency and NK-1 receptor selectivity. (PTX-0314.0001; PTX-321.0015.) The CP 96,345 compound, however, displayed species specificity, meaning that it was more effective in some species than in others. (PTX-313.0001; PTX-321.0015.)

53. Pfizer was not the only company working on NK-1 receptor antagonist compounds. After the publication of CP 96,345, many other companies began publishing and researching in the area, including major pharmaceutical companies such as Glaxo, Sanofi, and Rhone-Poulenc. (Tr. at 439:12-440:5, 815:24-816:8; see generally PTX-055; PTX-313; PTX-314; PTX-316; PTX-317; PTX-321; DTX-367; PDX-242; PDX-243.)

54. Against this backdrop, Merck began its own research program searching for highly potent and selective NK-1 receptor antagonist compounds that could be carried forward into safety

assessment testing with the hope of creating safe and effective drug products for clinical use. (Tr. at 624:4-625:1.) Merck internally referred to this research program as the “Substance P” project. (Tr. at 269:10-20.)

55. Merck’s internal Substance P project consisted of a large, crossfunctional team of chemists, biologists, pharmacologists, pharmaceutical scientists, and safety assessment scientists numbering between 70 and 90 people in total. (Tr. at 266:23-267:2, 624:12-17; PTX-150.0303.) Many team members contributed to different parts of the syntheses that occurred throughout the project. (Tr. at 247:21-25.)

56. With the exception of the limited information disclosed in Merck publications and publicly-available patent filings, the details of the substantial research conducted under Merck’s Substance P project remained largely confidential and was not available to the public in 1994. (Tr. at 161:25-162:4, 185:2-6, 631:8-13, 655:20-656:6, 688:14-16.)

57. The Merck Substance P project was located across three internal Merck sites: Terlings Park, United Kingdom; West Point, Pennsylvania; and Rahway, New Jersey. (Tr. at 624:17-20.) As of 1994, the four named inventors of the ’336 patent worked at the Rahway, New Jersey site. (Tr. at 624:17-20, 270:7-16.)

58. In the early 1990s, the Substance P project was filled with “days of ups and days of downs, there were setbacks, there was dead ends, there were lots of molecules that were made.” (Tr. at 267:3-6.) The large size of the Substance P project, however, allowed Merck to develop a large amount of internal proprietary information. (Tr. at 268:2-5.)

59. To begin the Substance P project, scientists in the Merck medicinal chemistry group worked on identifying lead classes of compounds they could use to develop proprietary compounds with the ultimate goal of proposing them as potential drug candidates. (Tr. at 624:21-625:1.) This

process began before Dr. MacCoss's team became involved with the project, and Merck gained internal experience and knowledge about NK-1 receptor antagonism in that time. (Tr. at 234:9-235:3.)

60. Dr. Hale estimated that the Merck scientists collectively synthesized at least a thousand compounds in the Substance P project. (Tr. at 625:2-8; see also Tr. at 262:25-263:8.) Dr. MacCoss described the Substance P project as "probably one of the biggest efforts we had put on a project." (Tr. at 234:14-15.)

61. Merck's medicinal chemists began their search for proprietary lead compounds by using two divergent methods: compound screening (e.g., PDX 503) and chemical modifications (e.g., PDX 504).

62. In the course of this work, Merck's medicinal chemists made many different structures including compounds from the lead series quinuclidine, piperazine, cyclohexane, pyran, imidazole, morpholine, and piperidine. (Tr. at 632:14-20; PDX-504.)

63. Merck scientists conducting chemical modifications were able to discover the confidential and proprietary compound L-742,694 ("the '694 compound"), which Merck decided to test for safety in the hopes of developing it for clinical use. (Tr. at 632:14-20; PDX-504.)

64. The '694 compound is not the compound that ultimately became known as aprepitant, nor is it the compound that ultimately became known as fosaprepitant. (Tr. at 632:21-633:1.) The '694 compound was synthesized to contain phenyl rings – particularly the bis(trifluoromethyl)phenyl and 3(S)-phenyl rings – that Merck discovered through its confidential internal testing to be important for interaction with NK-1 receptors. (Tr. at 635:22-636:4.)

65. In an attempt to minimize some of the observed toxic side effects found in its other, less advanced Substance P compounds, Merck scientists synthesized the '694 compound with a

morpholine core. (Tr. at 636:5-8.) The '694 compound was synthesized with a triazolone substituent with the hope of imparting favorable *in vivo* properties such as good potency and good duration of action. (Tr. at 636:8-15.). The '694 compound was further synthesized with specific "2(S), 3(S)" stereochemistry (nomenclature used to describe the compound's three-dimensional structure) with the hope of imparting favorable properties. (Tr. at 636:16-23.)

66. However, after safety testing, Merck scientists determined that the '694 compound, which had poor water solubility, also cause liver weight gain and elevated liver enzymes in rats. (Tr. at 637:2-10, 640:12.) Dr. Hale interpreted these results as meaning that chronic administration of the '694 compound could cause liver toxicity in rats. (Tr. at 640:10-12.)

67. Dr. Hale and the medicinal chemists in the Substance P group developed a hypothesis (not based on the prior art) that the '694 compound's toxicity followed from the way that the compound was being metabolized in rats, specifically that the liver had to work hard to metabolize the compound. (Tr. at 641:14-21.)

68. Dr. Hale synthesized new morpholine compounds based on ideas he had regarding where on the '694 compound he thought metabolism would occur. In August 1993, this work resulted in his design and synthesis of a compound that Merck referred to internally as "L-754,030," ("the '030 compound"), which was shown to have addressed the toxicity issues. (Tr. at 642:6-20.) The '030 compound is known today as aprepitant. (Tr. at 642:21-22.)

69. Dr. Hale was the Merck medicinal chemist who conducted the final step to synthesize the '030 compound for the first time on August 25, 1993. (Tr. at 643:5-16; PTX-186.0185.) This consisted of an eleven step process which Dr. Hale estimated would take approximately four weeks from start to finish to make in small quantities (i.e., gram amounts) sufficient for the kind of testing done in a discovery setting. (Tr. at 643:20-644:2.)

70. On December 12, 1993, the Merck scientists submitted an internal and confidential report to the RMC providing detailed chemical, biological, and toxicological data characterizing the '030 compound, and recommending that the '030 compound be approved to be advanced into further animal toxicity studies needed as a precursor to human studies. (Tr. at 484:18-485:6, 655:6-656:9; PTX-150.0002.) The information regarding the '030 compound in this RMC report was not available in the prior art as of 1994. (Tr. at 485:2-6, 656:7-9.)

71. Among other things, the RMC report for the '030 compound described Merck's internal and confidential testing showing that the '030 compound had poor aqueous solubility. (Tr. at 644:3-7; PTX-150.0298-300.) On December 23, 1993, Merck's RMC gave "conditional" approval to the '030 compound as a "backup" to the '694 compound for purposes of potential commercial development. In particular, the RMC required that Merck scientists try to find a new compound that could be administered both orally and intravenously. (Tr. at 759:19-23, 763:4-16; DTX-039.0006.) The medicinal chemists of the Substance P program embarked upon efforts to synthesize other compounds that had better water solubility than the '030 compound, in the hopes of obtaining a potent NK-1 receptor antagonist compound that would be suitable for oral and intravenous administration. To this aim, Dr. MacCoss oversaw a research effort at Terlings Park to make structural modifications with the intention of introducing substituents that would maintain the compound's favorable properties but also increase solubility. (Tr. at 644:12-645:3.)

72. Dr. MacCoss also championed a research effort at the Rahway, New Jersey site of trying to make structural modifications with the hope of achieving water-soluble compounds that would act as prodrugs in the body. (Tr. at 645:4-17, 646:3-11.)

73. Merck scientists within the Substance P program, including groups outside the medicinal chemistry department, also looked at other potential methods of modifying the '030

compound for use in oral and intravenous administration, including making salt forms and testing different formulation technologies. (Tr. at 290:25-291:5, 645:18-25, 811:7-9.)

74. Dr. MacCoss testified that term “prodrug” is a complex term that can apply to a number of different entities and concepts. (Tr. at 229:9-12.) Dr. Sherman testified that, even as of 2013, there were a “limited number of individuals in the United States with experience and expertise in evaluating and explaining the concepts involved in the synthesis of prodrugs such as fosaprepitant.” (Tr. at 201:19-25; see also 328:5-6.)

75. Dr. MacCoss testified that research efforts concerning prodrugs was not Merck’s preferred approach, and that Merck was instead trying to modify the ’030 “molecule itself to make it more water soluble, that was done by the Terlings Park group in the U.K.” (Tr. at 271:9-21, 290:7-10.)

76. In particular, contemporaneous with Merck’s efforts to attempt to make prodrugs, there were extensive efforts from the Terlings Park chemists on the Substance P team to do structural modifications to some of Merck’s lead compounds to include water-solubilizing substituents. (Tr. at 697:11-698:1, 786:12-16, 803:16-25; PDX-505.)

77. Out of the numerous compounds that the Terlings Park scientists synthesized in attempting to incorporate water-solubilizing substituents into the ’030 compound, the compound L-759,274 (“the ’274 compound”) became a compound of significant interest. (Tr. at 697:21-698:19; PDX-505.) However, due to some toxicity issues, the ’274 compound was not developed further. (Tr. at 699:5-11.)

78. Prior to having made and tested these potential prodrug compounds with added phosphoryl groups, it was not clear to the Merck scientists at that time whether any of the resulting compounds would be soluble in water enough to be used intravenously, or even soluble at all. (Tr.

at 303:18-24.) Also, prior to having made and tested these compounds, it was not clear to the Merck scientists at that time whether any of these compounds would work as a prodrug in a biological environment. (Tr. at 296:9-16.) Dr. Mills testified that, in attempting to make a prodrug, trying to achieve that exact balance between stability and ability to release the parent drug as “something that was not predictable ahead of time, [and] required much experimentation.” (Tr. at 804:2-14, see also Tr. at 296:17-24.)

77. Dr. Hale and Dr. Dorn were assigned by Malcolm MacCoss and Sander Mills to work on trying to make prodrugs. (Tr. at 646:3-11, 650:8-14; PTX-153.) Dr. MacCoss suggested attempting prodrugs, with a promoiety that would cleave *in vivo*, based on his years of experience, understanding, and knowledge of the stability of various types of bonds. (Tr. at 254:17-25.)

78. Using Merck’s confidential information learned through the iterative process of drug design, Dr. Hale and the Substance P project medicinal chemists thought about the triazolone moiety of the ’030 compound as one substituent that they could try to modify in attempting to make a prodrug. (Tr. at 255:23-256:25, 646:12-647:14; PTX-186.0185.)

79. The prodrug efforts of the Substance P project guided by Dr. MacCoss began at least as early as December 10, 1993, even before RMC’s issuance of conditional approval for the ’030 compound. In particular, at least as of December 10, 1993, Dr. Dorn was attempting to make prodrug compounds using the ’694 compound, although the investigations conducted by Dr. Dorn involved far different chemical structures than those seen in fosaprepitant dimeglumine. (Tr. at 284:19-285:15, 650:15-20, 650:25-651:4, 651:21-652:2, 654:8-20, 655:1-5; PTX-153.0002-4; PTX-190.0002, 202-209.)

80. Though Dr. Hale intended to attempt to synthesize prodrugs of the ’030 compound, Dr. Hale, like Dr. Dorn, did not start his research by attempting prodrug chemistry on the ’030

compound itself because of the lengthy period of time it would have taken to synthesize that compound for chemistry research. Instead, Dr. Hale used the stockpiles of '694 compound that, by virtue of the prior submission of that compound for toxicity testing, had been synthesized in large quantity (i.e., kilogram amounts) during its development. (Tr. at 647:15-648:8.) Dr. Hale thought he could use the '694 compound for his initial experimentation because it shared the same triazolone moiety as on the '030 compound. (Tr. at 648:9-12; compare PTX-179.0003 with PTX-150.0020.)

81. The large internal stockpiles of the '694 compound for use in initial investigations provided Drs. Hale and Dorn an effectively unlimited and free source of starting compound that allowed him to explore and investigate chemistry, without having to take four weeks at a time to synthesize more '030 compound for his investigations. (Tr. at 647:19-648:12, 648:18-649:5, see also 286:18-287:3.)

82. Dr. Hale began his efforts at synthesizing prodrugs with the '694 compound on January 3, 1994, after receiving ideas conveyed to him by Dr. MacCoss. (Tr. at 660:13-23; PTX-186.0257.) In particular, Dr. MacCoss educated Drs. Hale and Dorn about the prodrug fosphenytoin, which had a phosphate group attached to a methylene linker. (Tr. at 651:4-17.)

83. The compound now known as fosaprepitant was first synthesized on January 31, 1994. The process used by Dr. Hale to synthesize fosaprepitant involved many experiments, and many failures. Standard methods of purification of the compound failed him, making synthesis of a pure product for testing much more complicated. (Tr. at 673:6-24; PTX-186.0275.)

84. It was only after performing high performance liquid chromatography ("HPLC") during the reaction—something not commonly performed by medicinal chemists at that time during experimentation—that Dr. Hale was able to better understand the chemical transformations.

(Tr. at 675:23-677:9.) From his reaction on January 31, 1994, Dr. Hale obtained 230 milligrams of product with a purity of 89.6%, which he viewed as pure enough to start characterizing the compound but, but not sufficiently pure to obtain reliable results from biological testing. (Tr. at 677:7-18, 678:17-22; PTX-186.0279-80.) The product of Dr. Hale's January 31, 1994 reaction sequence was the dipotassium salt of L-758,298, or the '298 compound, which subsequently became known as fosaprepitant. (Tr. at 677:19-25; PTX-186.0279-80.)

85. Also on January 31, 1994, Dr. Hale again attempted to make more '298 compound from the '030 compound, this time using different purification methods to get an even purer product – but this experiment failed. (Tr. at 678:23-679:25; PTX-186.0281.)

86. Several more months of experimentation was necessary to make a form of fosaprepitant that did not degrade quickly over time. The evidence at trial established that fosaprepitant dimeglumine was synthesized by April 29, 1994, and a full set of *in vitro* and *in vivo* data existed with respect to the compound by September 1, 1994. (Tr. at 693:20-694:8, 695:12-21; PTX-187.0072; PTX-184.0002.) Ultimately, Dr. Dorn's research on salt forms led to the dimeglumine salt of fosaprepitant, which the Merck scientists found to be stable enough to be further studied as a candidate to become a marketable drug. (Tr. at 791:13-20.)

87. On September 1, 1994, the '298 compound as a dimeglumine salt was submitted to the RMC for approval to take the compound into further development. (Tr. at 695:15-20; PTX-184.0002.) The '298 compound dimeglumine salt, referred to now as fosaprepitant dimeglumine, was subject to extensive pre-clinical toxicity studies to qualify for clinical investigations and was approved by the FDA as EMEND® for Injection. (Tr. at 699:25-700:8.)

88. Dr. MacCoss explained that fosaprepitant dimeglumine was discovered to be stable enough for formulation and storage but, when introduced into a human, it would be cleaved either enzymatically or chemically back to the '030 compound. (Tr. at 262:12-23.)

89. Synthesis of the dimeglumine salt of the '298 compound was a 13-step process, which would take Dr. Hale between six and eight weeks to synthesize in small quantities from start to finish. (Tr. at 688:17-25.)

90. Molecules are comprised of atoms bonded together with covalent bonds. Like a spring between the two atoms, a covalent bond allows the atoms to move but does not allow them to separate from one another. (Tr. at 423:16-424:7.)

91. Dr. Roush explained how fosaprepitant dimeglumine is an entirely new compound – with its own chemical properties like robust stability, and its own *in vitro* biological activity – which then interacts with enzymes in the body to break down into another active molecule. (Tr. at 423:9-15, 430:5-19, 433:1-8.) Many other conventional drug compounds break down or metabolize in the body, and despite this they are still considered to be chemical compounds in their own right. (Tr. at 465:2-12.)

92. As Dr. Roush explained at trial, the Asserted Claims are not just claims to a salt, but rather are directed to the dimeglumine salt of a new covalently bonded molecule (fosaprepitant), which acts in the body as prodrug following administration. (Tr. at 423:20-424:18; PTX-001.0081-82; PTX-160.0004.) Dr. Sherman agreed that a prodrug is not a salt and that it contains covalent bonds. (Tr. at 98:4-99:9, 201:16-18.)

#### **E. The Claimed Compound And The Prior Art**

93. The Asserted Claims of the '336 patent specifically claim the new chemical compound, fosaprepitant dimeglumine, which is a chemical compound synthesized, isolated, and

purified by Dr. Hale and Dr. Dorn, with the assistance of Dr. Mills, and prompted and overseen by Dr. MacCoss. (Tr. at 96:7-21, 510:21-25; PTX-001.0001, 81-82.)

94. The contents of the '336 patent itself do not qualify as prior art in this litigation. (Tr. at 156:23-25.)

95. In the year 2000, a paper authored by Dr. Hale and other Merck scientists was published in the Journal of Medicinal Chemistry. The paper concluded that “an unprecedented prodrug strategy was undertaken and the N-phosphoryl derivative of [the '030 compound] was targeted as an entity with the potential to be metabolically converted *in vivo* to [the '030 compound].” In the 15 years since this article published, and aside from the generic litigation context, no person has ever challenged the accuracy of that statement. (Tr. at 789:1-13.)

96. The perspective of a POSA in 1994 was very different from that of the Merck researchers because the POSA did not have the benefit of all the Merck research into NK-1 receptor antagonist compounds commencing in 1991. (Tr. at 163:24-164:7, 688:14-16.)

97. Dr. Roush and Dr. Sherman have agreed, and the Court finds, that for the purposes of the '336 patent, a person of ordinary skill in the art has a Bachelor of Science degree or a higher degree, such as a Master's or a Ph.D. in chemistry or pharmaceutical science; and secondly, has several years of experience in development of pharmaceutical compositions, with several years meaning roughly three years. (Tr. at 438:13-23.) The person of ordinary skill in the art is that of a generalist of modest skill; there is nothing within the level of skill in the art that requires specialized expertise in any subfield. (Tr. at 438:24-439:2.)

98. In 1994, there were numerous references available to a POSA regarding compounds described as having NK-1 receptor antagonist activity. Dr. Roush presented over 40 exemplary prior art documents concerning NK-1 receptor antagonist compounds that were available to a

POSA in 1994. (Tr. at 439:12-440:5; see generally PTX-055; PTX-313; PTX-314; PTX-316; PTX-317; PTX-321; DTX-367; PDX-242; PDX-243.)

99. A POSA in 1994 would have known that the class of NK-1 receptor antagonists was associated with a large number of potential utilities (i.e., potential medical uses). For example, a 1993 review article by Maggi *et al.* (PTX-321)<sup>2</sup>, among other things, disclosed potential therapeutic applications for NK-1 receptor antagonists in: analgesia; headache; neurodegenerative movement and affective disorders; multiple sclerosis; control of inflammatory reactions and smooth muscle contractility; treatment of edema caused by thermal injury in humans; neurogenic inflammation at joint and visceral level; rheumatoid arthritis; chronic inflammation which underlies asthma; allergic rhinitis; Crohn's disease and ulcerative colitis; ocular inflammatory diseases; control of exaggerated gut motility in diseases such as irritable bowel syndrome; secretory diarrhea; cystitis; and regulating urinary bladder motility. (Tr. at 441:18-443:15, 445:18-446:2; PTX-321.0038-44.) Dr. MacCoss testified that there were a number of different potential diseases that one could contemplate using a Substance P antagonist to treat. (Tr. at 273:15-17.)

100. Additionally, publications and published patent applications from Glaxo in 1993 illustrated that NK-1 receptor antagonists were potentially useful in the treatment of emesis, in addition to being known as potentially useful for "a variety of disorders including pain, inflammatory diseases, allergic disorders, CNS disorders, skin disorders, cough and gastrointestinal disorders such as ulcerative colitis and Crohn's disease." (Tr. at 443:16-24, 445:18-446:2; DTX-367.0002; PTX-316.0003.)

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<sup>2</sup> Maggi et al., *Tachykinin Receptors and Tachykinin Receptor Antagonists*, 13 J. AUTON. PHARMACOL. 23 (1993).

101. Dr. Sherman agreed that in 1994, a POSA would have been aware of published work by Pfizer, Sanofi, and other companies who were working on NK-1 antagonist compounds at the time. (Tr. at 174:4-8.)

102. A POSA looking at the prior art in 1994 would have found that one potential starting point in the field of NK-1 receptor antagonists was a Pfizer compound known as CP-99,994, as featured in a 1992 publication by Desai *et al.* (PTX-314)<sup>3</sup>, titled “Discovery of a Potent Substance P Antagonist: Recognition of the Key Molecular Determinant.” (Tr. at 447:13-18; PTX-314.0001.)

103. As a POSA would have understood from Desai *et al.* (1992), CP-99,994 was the next step forward from an earlier series of Pfizer NK-1 antagonist compounds. (Tr. at 446:17-25.) A POSA would have further understood from Desai *et al.* (1992) that CP-99,994 was “the most potent [Substance P] antagonist yet discovered,” as demonstrated by NK-1 receptor binding data for that compound in Desai *et al.* (1992). (Tr. at 447:13-18, PTX-314.0001.)

104. Dr. Sherman agreed that CP-99,994 was a potent NK-1 receptor antagonist compound, as disclosed by Pfizer in the prior art. (Tr. at 174:9-12.)

105. A POSA in 1994 reviewing the NK-1 receptor antagonist prior art would have also learned from documents including the published EP '280 application (PTX-316)<sup>4</sup> and Bountra *et al.* (DTX-367)<sup>5</sup> both published in 1993, that Glaxo had studied CP-99,994 in a ferret animal model

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<sup>3</sup> Desai *et al.*, *Discovery of a Potent Substance P Antagonist: Recognition of the Key Molecular Determinant*, 35 J.MED. CHEM. 4911 (1992).

<sup>4</sup> European Patent Office Publication No. 0,533,280 A1.

<sup>5</sup> Bountra *et al.*, *Anti-Emetic Profile of a Non-Peptide Neurokinin NK1 Receptor Antagonist, CP-99,994, in Ferrets*, 249 EUR. J. PHARMACOL., at R3 (1993).

for the treatment of emesis, and had demonstrated its ability to inhibit emesis in the ferret model, over a range of different emesis-inducing agents. (Tr. at 447:21-448:6, 449:3-13; PTX-316.0023; DTX-367.0002.)

106. A POSA in 1994 would thus have understood that others in the NK-1 receptor antagonist field, including Glaxo, were quite interested in Pfizer's CP-99,994 compound. (Tr. at 447:21-448:6, 449:3-13.)

107. Glaxo also made and tested its own NK-1 receptor antagonist compound, described in Glaxo's EP '280 application as Example 1, which like Pfizer's compound, was shown to be effective in the *in vivo* ferret emesis model and was another potential starting point for further development. (Tr. at 449:14-24; PTX-316.0023.)

108. Prior to 1994, Glaxo, a pharmaceutical company, was publishing literature on NK-1 receptor antagonist compounds in the prior art. In fact, Glaxo published actual data reporting that the compounds inhibited cisplatin-induced emesis in an animal model. (Tr. at 174:25-175:10.)

109. Another potential starting point for an NK-1 receptor antagonist that a POSA in 1994 could have considered was a Sanofi compound known as SR140333, as described in a 1993 article by *Emonds-Alt et al.* (PTX-313)<sup>6</sup> titled "*In vitro* and *in vivo* biological activities of SR140333, a novel potent non-peptide tachykinin NK1 receptor antagonist." (Tr. at 450:5-13; PTX-313.0001.)

110. As a POSA would have understood from data reported in *Emonds-Alt et al.* (1993), SR140333 was a new compound that was a selective and highly potent antagonist of NK-1 receptors from various species, including humans. *Emonds-Alt et al.* (1993) included actual

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<sup>6</sup> Emonds-Alt et al., *In Vitro and in Vivo Biological Activities of SR140333, a Novel Potent Non-Peptide Tachykinin NK1 Receptor Antagonist*, 250 EUR. J. PHARMACOL. 403 (1993).

receptor binding affinity data showing the selective and potent antagonist activity of SR140333 for NK-1 receptors. (Tr. at 450:20-451:12; PTX-313.0005.)

111. *Emonds-Alt et al.* (1993) also provided *in vivo* animal data showing “highly potent antagonism” of NK-1 receptors by SR140333, including in models of hypotension, bronchoconstriction, and plasma extravasation. (PTX-313.0009-10.) *Emonds-Alt et al.* (1993) further explained that “[t]his highly potent antagonism was obtained whatever the animal species used.” (PTX-313.0010.)

112. Dr. Sherman agreed that Sanofi was a big drug company publishing literature on NK-1 receptor antagonist compounds in the prior art, and that Sanofi’s compound SR140333 was reported to be a highly potent antagonist of the NK-1 receptor of various species, including humans. (Tr. at 174:17-23.)

113. A POSA in 1994 looking at the prior art concerning NK-1 receptor antagonists would have also found a potential starting point in a compound from Rhone-Poulenc Rorer known as RPR 100893, which was described in a March 1994 article by *Tabart et al.* (PTX-055)<sup>7</sup>, entitled “Synthesis of RPR 100893, Prototype of a New Series of Potent and Selective Non Peptide NK1 Antagonists: The Triarylperhydroisoindolols.” (Tr. at 451:14-22; PTX-055.0004.)

114. As a POSA would have understood from *Tabart et al.* (1994), RPR 100893 was a “new potent, NK1 selective non peptide [substance P] antagonist, both *in vitro* and *in vivo*.” (PTX-055.0005.) *Tabart et al.* (1994) provided actual data demonstrating this activity, and noted that, unlike prior Rhone-Poulenc compounds that had the disadvantage of being less active against

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<sup>7</sup> *Tabart & Peyronel, Synthesis of RPR 100893, Prototype of a New Series of Potent and Selective Non Peptide NK1 Antagonists: The Triarylperhydroisoindolols*, 4 BIOORGANIC & MED. CHEM. LTRS. 673 (1994).

human NK-1 receptors than animal NK-1 receptors, RPR 100893 had “high affinity for human NK1 receptor.” (Tr. at 452:5-20; PTX-055.0004-5.)

115. Dr. Sherman agreed that Rhone-Poulenc, a big drug company, was publishing literature reporting NK-1 antagonist compounds in the prior art. (Tr. at 174:13-16.)

116. A further NK-1 receptor antagonist compound that a POSA in 1994 could have considered as a starting point was the Merck compound referred to as compound 7b in the 1993 publication *MacLeod et al.* (PTX-317)<sup>8</sup>, titled “N-Acyl-L-tryptophan Benzyl Esters: Potent Substance P Receptor Antagonists.” (Tr. at 452:21-453:4; PTX-317.0001.)

117. As a POSA would have understood from data reported in *MacLeod et al.* (1993), Merck considered compound 7b to be a highly potent NK-1 receptor antagonist, and that this and the other compounds described in *MacLeod et al.* 1993 “represent a novel structural class of substance P receptor antagonists and are highly potent leads for further optimization.” (Tr. at 453:12-454:2; PTX-317.0002.)

118. Compound 7b of *MacLeod et al.* (1993) is a different compound than compound 96 of the ’889 application and WO ’679 and compound 80 of WO ’440. (Tr. at 454:3-6.)

119. In addition to the above prior art documents regarding Pfizer’s compound CP-99,994, Glaxo’s Example 1, Sanofi’s SR140333, Rhone-Poulenc Rorer’s RPR 100893, and Merck’s compound 7b, the prior art contained numerous other documents with at least some actual biological data about individual NK-1 receptor compounds. None of these documents includes the compound selected by Dr. Sherman as a starting point for further modification.

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<sup>8</sup> *MacLeod et al., N-Acyl-L-Tryptophan Benzyl Esters: Potent Substance P Receptor Antagonists*, 36 J.MED. CHEM. 2044 (1993).

120. In addition, many of the documents available to a POSA in 1994 did not contain biological data specific to individual compounds. For instance, the '889 application, the WO '679 application, and the WO '440 application were among a larger set of documents that had no biological data specific to any compound. (Tr. at 458:3-23; PDX-243.) Moreover, it is undisputed that the patent examiner allowed the '336 patent to issue as a patent, even though WO '679 and WO '440 were of record. (Tr. at 195:4-7, 197:23-198:17.)

121. As of 1994, one of the authors who was deeply involved in Pfizer's work in the NK-1 receptor antagonist literature – Dr. Manoj Desai – had published a review discussing NK-1 receptor antagonist work, and that it had commented on a Merck compound that was not compound 80 of WO '440 or compound 96 of the '889 application or WO '679. (Tr. at 177:20- 178:13, 178:23-179:5, 179:24-180:16.)

122. Sandoz did not elicit from Dr. Sherman testimony about the NK-1 receptor antagonist prior art as of 1994 beyond the Merck '889 application and WO '679, even though Dr. Sherman was aware of this issue prior to trial. (Tr. at 174:4-8, 177:6-11.) Accordingly, Dr. Roush's testimony regarding the full scope and content of the prior art for NK-1 receptor antagonists was unrebutted.

123. In 1994, a POSA looking at the available literature regarding prodrugs, such as a 1990 review article *Balant et al. (PTX-016)*,<sup>9</sup> would have understood that, as of that time, “most prodrugs ha[d] been synthesized starting from valuable and well known drugs.” (Tr. at 461:2-6; PTX-016.0008.)

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<sup>9</sup> Balant et al., *Prodrugs for the Improvement of Drug Absorption Via Different Routes of Administration*, 15 EUR. J. DRUG METABOLISM & PHARMACOKINETICS, No. 2, at 143 (1990).

124. In 1994, compound 96 was not a “valuable and well known drug.” Given the state of the prior art, a POSA in 1994 would not have understood compound 96 to be a typical candidate for prodrug development as contemplated by literature such as *Balant*. (Tr. at 461:2-9.)

125. Dr. Sherman could not think of a single example, prior to 1995, of a POSA starting with a compound knowing its chemical name, its general mechanism of action, but having no data specific to that compound, and then modifying that compound into a prodrug. (Tr. at 209:10-210:1.)

126. Dr. Sherman confirmed that “aprepitant” was not marketed or known publicly as a drug in 1994. (Tr. at 164:16-18.) Accordingly, Dr. Sherman did not cite any public use of “aprepitant” or compound 96 in 1994, or any reports of people being treated with “aprepitant” or compound 96 as of 1994. (Tr. at 167:23-168:4.)

127. A POSA in 1994 would have further understood from literature such as *Balant* that, in general, one should not start to develop a new prodrug from a prior compound without at least the benefit of having well-studied pharmacokinetic and biological data for that compound. (Tr. at 461:10-462:5; PTX-016.0007; see also 465:13-466:5.)

128. In 1994, a POSA would not have had access to well-studied pharmacokinetic and biological data for compound 96. (Tr. at 167:23-168:4.) To the extent specific data regarding the activity or pharmacokinetics existed as of 1994, it was in confidential data internal to Merck, and not available to a POSA. (E.g., Tr. at 466:2-8, 478:2-10, 485:2-6, 493:10-15, 498:13-24.)

129. Dr. Sherman confirmed that the prior art did not disclose any pharmacokinetic data with respect to compound 96. (Tr. at 168:5-7.)

130. In 1994, a POSA would have considered prodrugs to be active ingredients that provided pharmaceutical efficacy upon administration. For example, prodrugs known to a POSA

in 1994 such as aspirin, codeine, omeprazole, and pantoprazole would have been considered active ingredients in drug products. (Tr. at 462:7-23.)

131. If a POSA in 1994 were to consider attempting to make a prodrug, they would have understood that they would face numerous points of possible failure in his or her research. A POSA would have especially been concerned about the possibility of failure if the starting point was not a well-studied compound with a significant amount of information available about it in the prior art. (Tr. at 462:24-463:18, 464:13-466:5.)

132. For example, a POSA in 1994 would have understood that an attempt to make a new prodrug compound might fail at the stage of chemical synthesis – i.e., difficulty in actually making the new prodrug compound in the first instance. This point of failure is especially likely if the POSA viewed the efforts as involving complex chemistry. (Tr. at 463:8-10.)

133. A POSA in 1994 would have known that another potential point of failure for making a new prodrug compound is that the prodrug has problematic stability. As a POSA would have understood, the prodrug would have to be suitably stable prior to administration so as to remain in its original form. (Tr. at 463:12-18; PTX-016.0007; PTX-019.0001.)

134. In 1994, a POSA would have also been concerned that an attempt to make a prodrug might fail because, following administration to a patient, the new prodrug compound might not convert to its active moiety in the body in a manner that provides the desired therapeutic activity. For example, for a new prodrug compound, a POSA might not know whether the body contained the right machinery (i.e., enzymes) to provide this conversion to the active form. (Tr. at 464:14-465:1; PTX-016.0007.)

135. A POSA in 1994 would have thus been concerned about the rate of conversion for an attempted prodrug, if it converted at all, because that impacts the efficacy of the prodrug itself.

As explained in *Balant*, “[t]he *in vivo* lability should be sufficient to permit a release of the active moiety at a rate adequate to ensure its therapeutic activity.” (PTX-016.0007.) The prior art also explained that, typically, prodrugs should “be converted quantitatively and rapidly *in vivo* into the active parent drug” (PTX-019.0001 (emphasis added)), and that a water-soluble prodrug for injection should be “converted rapidly to the active parent drug after injection” (PTX-015.0001 (emphasis added)). (Tr. at 497:5-498:4.)

136. Additionally, a POSA in 1994 would have been concerned that, as *Balant* explained, “the modification of one pharmacokinetic property, frequently alters other properties of the drug molecule and caution must thus be exercised when embarking on a program of this nature.” (PTX-016.0007.)

137. For example, a POSA in 1994 would have understood that because the prodrug itself is a new chemical compound with its own properties, depending on the manner of conversion, the body would potentially face the situation of “polypharmacology” – that is, where two chemical compounds may have their activities against different targets, and their own metabolic chemistries that might break down to yield active or toxic metabolites in the human body. (Tr. at 291:6-13, 320:14-22, 465:2-466:1, 497:5-498:4.)

138. A POSA would have been especially concerned about complexity and the potential for failure in synthesizing a prodrug where the parent compound to which the prodrug converts is also not a well-studied compound. (Tr. at 465:2-466:5.)

139. Thus, given that there were no biological or pharmacokinetic data specific to compound 96 available in the prior art as of 1994, had a POSA in 1994 somehow wound up with compound 96 as a starting point for further development, a POSA would have had no idea where

to go or where to begin in attempting to make a new compound that acts as a prodrug. (Tr. at 477:22-478:10.)

140. A POSA in 1994 would have understood that there was a very large universe of potential prodrugs that do not involve phosphoryl groups. (Tr. at 477:18-21.)

141. None of the alleged prior art disclosed, taught or suggested to a POSA in 1994 the structure of fosaprepitant dimeglumine, or that the compound, if made, would perform as a prodrug. (Tr. at 422:6-11, 494:15-22.)

142. For instance, Sandoz presented *Murdock et al.* (1993) (PTX-040), as prior art relevant to the '336 patent. *Murdock et al.* involved certain prodrugs of basic nitrogenous compounds. *Murdock et al.* (1993) would have been understood by a POSA in 1994 to concern certain prodrugs that were made from compounds with *basic* (as opposed to *acidic*) nitrogenous groups, as the reference discusses. (Tr. at 471:14-472:12, 476:13-22; PDX-253; PTX-040.0001.)

143. The specific prodrugs discussed in *Murdock et al.* (1993) were made from the compound bisantrene. At the time of *Murdock's* publication, bisantrene, unlike compound 96, had been a well-studied, clinically tested drug known for at least 10 years prior to *Murdock's* work. (Tr. at 466:22-467:12; PTX-040.0001.) Moreover, bisantrene, the compound in *Murdock*, was a treatment for cancer, and was not an NK-1 receptor antagonist or a compound used for the treatment of emesis. (Tr. at 144:9-15, 144:20-145:2, 145:9-12.)

144. The problem stated in *Murdock et al.* (1993) was that, while bisantrene was already known to be water-soluble as its hydrochloride salt and was clinically used in an aqueous intravenous formulation, bisantrene had the disadvantage of precipitating out of solution following injection. (Tr. at 467:5-19; PTX-040.0001.)

145. As described in *Murdock* et al. (1993), the first attempts to solve the problem faced by *Murdock* were not to try to make a prodrug. Instead, initial attempts included formulation efforts, namely salt formation, and formation of bisantrene into an emulsion. (Tr. at 467:24-468:5; PTX-040.0001-2.)

146. As stated in *Murdock* et al. (1993), after this initial work failed, the researchers sought a “slowly hydrolyzed” prodrug of bisantrene – i.e., a prodrug that would convert very gradually into the parent compound. As they stated, the researchers apparently hoped that such slow conversion might mitigate certain toxicity issues associated with the active anti-cancer drug, bisantrene. (Tr. at 468:6-18; PTX-040.0001.)

147. A POSA in 1994 reading *Murdock* et al. (1993) would have understood that the parent compound bisantrene contains two highly basic functional groups, known as “guanidino” groups. (Tr. at 468:19-469:4; PTX-040.0001-2.) These guanidino groups contain a central carbon atom bonded to three nitrogen atoms. (PTX-040.0001-2.)

148. In *Murdock* et al. (1993), a basic nitrogen position on one or both of the highly basic guanidino substituents was phosphorylated, yielding the bisphosphoryl compound numbered “6,” and the monophosphoryl compound numbered “9,” respectively. (Tr. at 469:5-22; PTX-040.0002.) A sodium salt was also prepared of the bis-phosphoryl compound 6, yielding the compound numbered “7.” (Tr. at 469:5-22; PTX-040.0002.) Another monophosphoryl compound was prepared that had an additional ethyl group, numbered “10.” (Tr. at 469:5-22; PTX-040.0002.)

149. Dr. MacCoss explained that there are different types of phosphoramidate bonds that depend on the nature of the nitrogen atom and what type of ring – if any – the nitrogen is in. (Tr. at 255:7-13.) Dr. MacCoss explained that there are different chemical drivers that determine the strength and stability of different phosphoramidate bonds. (Tr. at 255:14-22.)

150. Therefore, even if a POSA in 1994 selected compound 96 for modification, and further considered *Murdock* et al. (1993) at that time, the POSA would have understood that the bisantrene compound in *Murdock* is structurally very different from compound 96 of the '889 application and WO '679. A POSA in 1994 would not have reasonably expected that the N-phosphorylation technique used for *Murdock* would work for compound 96, in view of the differences between the bisantrene compound of *Murdock* and compound 96. (Tr. at 469:23-472:12.)

151. For example, as Dr. Roush explained, the compounds of *Murdock* and compound 96 have very different nitrogen-containing heterocycles, with opposite electronic effects, and accordingly, different chemical behavior and reactivity. Specifically, assuming a POSA looked at these compounds in 1994 as per Dr. Sherman's hindsight analysis, the POSA would have seen that *Murdock* has two guanidino substituents, each with a highly *basic* nitrogen position; while, in contrast, compound 96 has a triazolone substituent containing NH-*acidic* groups – i.e., the opposite reactivity. (Tr. at 469:23-471:5.)

152. As Dr. Roush explained, a POSA in 1994 would have understood that the highly basic nitrogen of bisantrene would likely have a strong negative charge, whereas the NH-acidic groups of compound 96 would have a weak positive charge. (Tr. at 471:6-472:12; PDX-253.)

153. As explained by Dr. Roush, in the case of compound 96, a POSA would have understood that the weak positive charge of the NH-acidic groups could repel the positive charge of the phosphorylating group –like the force repelling the positive poles of two magnets – thus making the NH-acidic groups unreactive. A POSA in 1994 would thus have not reasonably expected the N-phosphorylation technique of *Murdock* to work for compound 96, even if such

POSA had considered *Murdock* in connection with work surrounding an NK-1 receptor antagonist compound as Dr. Sherman opined. (Tr. at 471:6-25; 472:1-12; PDX-253.) Dr. Sherman also testified to this fact on cross-examination. (Tr. at 146:15-18.)

154. *Murdock* et al. (1993) reported the testing of its phosphorylated basic compounds in animal models, including to determine whether they would convert *in vivo* following administration, and whether they would have efficacy in animal models of cancer. The animal testing revealed that conversion of the prodrug to bisantrene required “several hours.” (Tr. at 473:10-16.)

155. *Murdock* et al. (1993) also reported data from stability testing of its phosphorylated basic compounds. A POSA in 1994 reading *Murdock* would have understood these data to show that chemical stability of compounds – including their salts – is unpredictable and complex. For example, *Murdock* reports that:

- the bisphosphorylated compound “6” is stable for more than 5 years, but its sodium salt “7” decomposed within 6 months;
- also in contrast to the stable bisphosphoryl compound “6,” the monophosphoryl compound “9” decomposed within 6 months; and
- in contrast to the relatively unstable monophosphoryl compound “9,” an N-ethyl derivative of that compound was stable for more than 1 year.

(Tr. at 474:1-18; PTX-040.0002.)

156. U.S. Patent No. 5,070,082 (“*Murdock* ’082 patent”) (PTX-063) describes the same slowly hydrolyzing phosphorylated prodrugs of bisantrene detailed in *Murdock* et al. (1993), as well as prodrugs for other “basic nitrogenous” compounds such as basic amines, amidines, and

guanidines. (Tr. at 475:20-476:4; PTX-063 at Abstract, col. 12:22-44, 13:6-15, 14:13-19, 17:6-18, 19:60-65, 21:25-30.)

157. Similar to *Murdock* et al. (1993), the Murdock '082 patent describes the patented subject matter as addressing the problem of injecting “basic nitrogenous drug compounds” that are water soluble as acid-addition salts, but precipitate in blood following injection. (PTX-063.0001, Abstract; col. 12:22-33, 14:13-19.)

158. A POSA in 1994 would have understood that, in the compounds of the Murdock '082 patent, the phosphoryl group is attached to basic nitrogen positions. (Tr. at 476:5-12; PTX-063 at col. 21:25-30.)

159. Of note, the unphosphorylated “NH” groups to either side of the center C=O group of the compound depicted above could be described as acidic NH groups, and yet the Murdock '082 patent does not operate to phosphorylate these groups. In this way, the chemistry discussed in the Murdock '082 patent confirms that it does not teach how to make N-phosphoryl prodrugs of NH-acidic groups. (Tr. at 476:13-19; PTX-063 at col. 21:25-30.)

160. In addition to the Murdock documents, a chapter from a 1992 textbook by *Silverman* (DTX-447)<sup>10</sup> relied on by Dr. Sherman in explaining the state of the art regarding prodrugs also discusses “prodrug analogs of amines.” (Tr. at 477:10-21; DTX-447.0008-9.)

161. In the section of the *Silverman* chapter regarding prodrugs of amines, there is no description of any prodrugs that involve phosphorylation of a nitrogen. (Tr. at 477:10-21; DTX-447.0008-9.)

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<sup>10</sup> Richard B. Silverman, THE ORGANIC CHEMISTRY OF DRUG DESIGN AND DRUG ACTION 352 (1992) (“*Silverman*”).

162. In contrast to the prodrugs of basic nitrogenous compounds described in *Murdock* et al. (1993) and the Murdock '082 patent, the literature as of 1994 included examples of prodrugs of compounds with NH-acidic groups, but these teach prodrug modifications different from fosaprepitant dimeglumine. For example, a POSA in 1994 could have considered a 1989 publication by Bundgaard et al. (PTX-019)<sup>11</sup>, entitled “A Novel Solution-Stable, Water-Soluble Prodrug Type for Drugs Containing a Hydroxyl or an NH-Acidic Group.” (Tr. at 463:19-24, 476:23-477:6; PTX-019.0001.)

163. Dr. Roush explained that Table II of *Bundgaard* describes a number of N-substituted prodrugs of several drugs containing NH-acidic groups, including allopurinol, theophylline, phenytoin, and chlorzoxazone. (PTX-019.0004.) *Bundgaard* describes these prodrug compounds as being made by first making the N-hydroxymethyl derivatives (N-CH<sub>2</sub>-OH) of the parent compounds, and then further modifying those derivatives into the prodrug compounds described in Table II. (PTX-019.0002, 4.)

164. Table II of *Bundgaard* also provides data showing that a number of these NH-acidic prodrug compounds convert rapidly in human plasma, e.g., 50% conversion in as little as 24 seconds (0.4 minutes). (PTX-019.0004.)

165. *Bundgaard* concludes that the prodrug moieties it describes “are shown to be a potentially useful biolabile and solution-stable prodrug type for drugs containing hydroxyl groups or NH-acidic groups . . . .” (PTX-019.0005.)

166. As Dr. Roush explained, a POSA reading *Bundgaard* in 1994 would have understood that it does not describe attaching a phosphoryl group directly to an NH-acidic group.

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<sup>11</sup> Bundgaard et al., *Communications to the Editor, A Novel Solution-Stable, Water-Soluble Prodrug Type for Drugs Containing a Hydroxyl or an NH-Acidic Group*, 32 J.MED. CHEM., No. 12, at 2503 (1989) (“*Bundgaard*”).

Thus, application by a POSA of the techniques taught in Bundgaard could not have resulted in the claimed compound of the Asserted Claims, fosaprepitant dimeglumine, in which a phosphoryl group is directly bonded to an NH-acidic group of a triazolone ring of an otherwise complex chemical structure. (Tr. at 464:7-12, 477:7-9; PTX-019.0001.)

167. On direct examination, Dr. Sherman relied on a 1985 article by *Anderson et al.* (PTX-015)<sup>12</sup> in support of his obviousness allegations regarding the claimed compound of the Asserted Claims, fosaprepitant dimeglumine. *Anderson et al.* (1985), however, did not disclose any compounds that are relevant to fosaprepitant dimeglumine, and Dr. Sherman did not offer any detailed substantive explanation of *Anderson* at trial. (Tr. at 122:10-24, 478:11-14, 478:24-479:9.)

168. As explained by Dr. Roush, *Anderson et al.* (1985) described the preparation of carboxylic acid ester prodrugs of the steroid methylprednisone, which were intended to overcome stability issues in solution faced by earlier ester forms, including phosphate esters of the drugs. (Tr. at 478:24-479:9; PTX-015.0001.)

169. The related patent, U.S. Patent No. 4,443,440 (“the Anderson ’440 patent”) (PTX-60), described carboxylic acid esters and other esters of steroids, and explained a number of challenges presented by phosphate esters, including (1) that they are “often difficult to purify and are frequently very hygroscopic,” (2) that they are most stable above pH 7, which raises other possible issues with drug degradation; and (3) precipitation of free corticosteroid may occur due to a limited amount of hydrolysis (i.e., before delivery to the patient), which can limit the shelf-life of the compound and thus limit its usefulness as a prodrug. (Tr. at 479:10-480:9; PTX-060,

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<sup>12</sup> *Anderson et al., Strategies in the Design of Solution-Stable, Water-Soluble Prodrugs II: Properties of Micellar Prodrugs of Methylprednisolone*, 74 J. PHARM. SCI., No. 3, at 375 (1985) (“*Anderson et al.* (1985)”).

col. 1, ll. 54-65.) Accordingly, the Anderson '440 patent is another example of the complexity of prodrug chemistry. (Tr. at 480:7-9.)

170. The phosphate ester prodrugs and other prodrugs referenced in Anderson et al. (1985) and the Anderson '440 patent are different from the type of prodrug compound claimed in the Asserted Claims of the '336 patent because, among other things, they do not involve the modification of a specific nitrogen atom of a triazolone ring in an otherwise complex molecule. (Tr. at 480:10-12; PTX-015.0001; PTX-060.0001-2.)

171. In its pretrial Contested Facts, Sandoz relied on a 1953 article by *Mosher* et al. (PTX-039)<sup>13</sup> in support of its obviousness allegations against the Asserted Claims. (D.I. 232 at 113, ¶¶ 199-203.) At trial, however, Sandoz did not elicit testimony from Dr. Sherman about Mosher. Dr. Roush explained, however, that Mosher further illustrates how a POSA in 1994 would have understood the attempted development of a prodrug to be a complex and unpredictable effort. (Tr. at 481:16-24; PTX-039.0002-3.)

172. *Mosher* described a failed attempt to generate a phosphate ester prodrug of the compound chloramphenicol, an antibiotic also known as chloromycetin. While a cyclic phosphate diester compound was prepared, the compound failed as a prodrug, because it was incapable of enzymatic hydrolysis, and thus failed to achieve any *in vivo* antibiotic activity. (Tr. at 481:16-24; PTX-039.0002-3.)

#### **F. Motivation To Modify Compound 96/Aprepitant**

173. Dr. Sherman stated on cross-examination that, prior to trial, he had utilized a lead compound analysis and focused on compound 96 of the '889 application and compound 80 of

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<sup>13</sup> Mosher et al., *The Phosphorylation of Chloromycetin*, 75 J. AM. CHEM. SOC'Y 4899 (1953) ("Mosher").

WO '440. (Tr. at 183:6-12, 185:2-6.) Namely, Dr. Sherman admitted that he “offer[ed] an opinion of obviousness based on a lead compound analysis” in his expert report in this case – selecting as a starting point of either compound 96 of the '889 application and WO '679, or compound 80 of WO '440. (Tr. at 183:6-17.) However, at trial, Dr. Sherman stated that this was not necessary.

174. Dr. Sherman admitted on cross-examination that a POSA in 1994 would have been guided by pertinent properties such as activity or potency, toxicity, or other relevant characteristics such as solubility in selecting starting points for further development from among the NK-1 receptor antagonist compounds. (Tr. at 184:8-22.) Dr. Sherman had testified prior to trial that such other relevant characteristics would include the cost of goods and the complexity of the synthetic route. (*Id.*) Notwithstanding this testimony, at trial, Dr. Sherman did not apply this guidance in analyzing what compound or compounds a POSA would have selected in 1994 as a starting point for further development as an NK-1 receptor antagonist. (Tr. at 185:2-6.)

175. As described above, and as explained by Dr. Roush, a POSA in 1994 would have been aware of many examples of highly promising NK-1 receptor antagonist compounds in the prior art with specific data on potency and other important properties, such as Pfizer's CP-99,994 (PTX-314); Sanofi's SR140333 (PTX-313); Rhone-Poulenc Rorer's RPR 100893 (PTX-055); Glaxo's Example 1 from EP '280 (PTX-316); and Merck's compound 7b from MacLeod et al. (1993) (PTX-317). (See *supra* § VI.A.)

176. Only two of the documents proffered at trial as prior art – the '889 application (DTX-016) and WO '679 (DTX-051) – contained any information about compound 96. These were merely two documents from among a number of documents in the prior art that contained no specific data distinguishing the activity of any individual NK-1 receptor antagonist compound. (Tr. at 164:8-11, 458:15-23; PDX-243.)

177. Dr. Sherman did not testify regarding any NK-1 receptor antagonist prior art as of 1994, beyond the disclosure of compound 96 in the '889 application and WO '679. (Tr. at 177:6-11.) Dr. Roush's extensive testimony regarding the scope and content of the prior art regarding NK-1 receptor antagonists was unrebutted.

178. A POSA in 1994, looking at the full scope of the NK-1 receptor antagonist prior art, would have viewed compounds such as Pfizer's CP-99,994, Sanofi's SR140333, Rhone-Poulenc Rorer's RPR 100893, Glaxo's Example 1, and Merck's compound 7b as having more promising activity and being more thoroughly studied than compound 96. In view of these other, highly promising compounds, a POSA would not have had any reason as of 1994 to select compound 96 as a starting point for further modification, particularly for commencing a research program directed at making new prodrug compounds. (Tr. at 441:6-17, 449:11-24, 450:8-13, 451:16-22, 453:12-20; PDX-243.)

179. Even if a POSA in 1994 were given compound 96 as a starting point, there was insufficient evidence that the POSA would have had a reason or motivation in the prior art to modify compound 96 specifically into the claimed compound of the Asserted Claims of the '336 patent, fosaprepitant dimeglumine.

180. As explained by Dr. Roush, a POSA in 1994 would not have known or predicted the solubility of compound 96 based solely on its structure. (Tr. at 482:23-490.3.) Dr. MacCoss explained that it is "impossible to answer" what makes compound 96 insoluble because solubility is "dependent upon the overall property of the molecule." (Tr. at 276:23-277:8.)

181. While today, it is known that compound 96 is extremely insoluble – like "cement dust" – that information was not disclosed in the prior art to a POSA in 1994. (Tr. at 484:18-

486:15, 493:14-15, 498:5-17.) As Dr. Roush testified, solubility is complex and unpredictable. (Tr. at 482:23-483:13.)

182. Nor would a POSA in 1994 have been motivated without hindsight to experimentally determine the solubility of compounds disclosed in prior art documents that had no specific biological or pharmacokinetic data, including the '889 application or WO '679, as such work would have been prohibitive. As Dr. Sherman admitted, supplies of compound 96 were not available to the public in 1994, and if a POSA wanted to test compound 96 or the other 600 enumerated compounds, such a person would first have to make all of them. (Tr. at 185:16-186:16.) And as explained by Dr. Hale – who was an inventor of compound 96 and had extensive personal, confidential experience with these compounds – in 1993 it would take him about four weeks to synthesize just compound 96 alone in quantities sufficient for testing. (Tr. at 643:8-644:2.)

183. Further, a POSA in 1994 searching for an NK-1 receptor antagonist compound suitable for IV administration would not have been motivated to search for insoluble compounds, or to use an extremely insoluble compound (e.g., compound 96) as a starting point if its solubility were somehow known. A POSA would have been motivated to turn to NK-1 receptor antagonist compounds as starting points that were disclosed in the art as potent and having more promising solubility. For example, Sanofi's SR140333 – described in the prior art as highly potent NK-1 receptor antagonist *in vitro* and *in vivo* – was also described as being dissolved in water and administered intravenously to dogs. (Tr. at 490:4-17; PTX-313.0002, 4; see *supra* § VI.A.)

308. Even if, as Dr. Sherman alleged, a POSA in 1994 were motivated to modify compound 96 for an intravenous formulation, the POSA would not have obviously decided to attempt making a

prodrug, but instead would have considered a number of other options, given information available in the prior art. (Tr. at 490:18-492:12.)

184. A POSA in 1994 following Dr. Sherman's proposed pathway with compound 96, given the limited information available in the prior art, could have considered options including:

- Making salt forms to try to increase solubility;
- Making a lipid emulsion (e.g., oil/water) that could be administered IV;
- Other formulation techniques to increase solubility such as micronization;
- Making different crystal forms or amorphous forms that might have enhanced solubility; and
- Making chemical substituent modifications in an attempt to increase solubility.

(Tr. at 490:18-492:12.)

185. For example, in *Murdock et al.* (1993), the authors explained that, prior to trying to make a prodrug of bisantrene in an attempt to make it more soluble, other approaches had been tried including formation of lactate salts and formulation as an emulsion. (Tr. at 467:20-468:5; PTX-040.0001-2.)

186. The evidence adduced at trial did not establish that a POSA in 1994 would have rejected the above approaches to increasing solubility of compound 96. Sandoz's expert has, in fact, presented contradictory evidence. While, on the one hand Dr. Sherman testified that substituent modifications would have been an unattractive option – relying on the hindsight knowledge of how long he believes it took Merck's internal researchers to invent fosaprepitant – (Tr. at 136:4-15), he also admitted that he has previously opined in this case that a POSA would have performed substituent modifications on compound 80 of WO '440 (to change it into compound 96). (Tr. at 170:3-8, 170:13-171:6, 173:14-25, 493:16-494:14; PTX-092.)

187. Selecting from among the various potential approaches would have been particularly complex and challenging for a POSA in 1994, given the lack of specific data in the prior art regarding the pharmacokinetic and biological properties of compound 96. The POSA would have thus been facing a multitude of options in the dark. (Tr. at 492:23-493:9.)

188. In particular, as noted above, a POSA would have understood from the prior art that (1) prodrugs were typically made from “valuable and well known drugs” – which compound 96 was not at that time; and that (2) one should not start development of a new prodrug compound without the benefit of well-studied pharmacokinetic and biological data for that compound – which did not exist in the prior art for compound 96, and existed only as confidential data internal to Merck. (Tr. at 461:2-9; PTX-016.0008.) In view of this uncertainty and complexity, a POSA in 1994 would not have been motivated to make a prodrug of compound 96.

**G. Motivation To Create The Claimed Compound**

189. A POSA in 1994 would have understood that the Murdock documents (PTX-040 and PTX-063) describe chemistry for “basic nitrogenous compounds” and this would not be transferable to making a prodrug of compound 96 (a compound with NH-acidic groups). (Tr. at 471:14-472:12, 476:13-22; PDX-253; PTX-040.0001.)

190. No evidence was offered as to why a POSA attempting to make a prodrug of compound 96 in 1994 would have turned to the chemically distinct compounds of *Murdock* for a teaching to modify compound 96, when the prior art literature described categories of prodrug moieties specific for NH-acidic compounds – which, if successfully applied to compound 96, would have resulted in a compound different from fosaprepitant dimeglumine. (Tr. at 463:19-24, 476:23-477:6; PTX-019.0001.)

191. A POSA in 1994 would have been aware that the bisantrene prodrug described in *Murdock* et al. was intentionally made to provide slow conversion back to the parent drug bisantrene, to avoid toxic effects of the anti-cancer drug. (Tr. at 468:6-18; PTX-040.0001.) Murdock therefore experimentally confirmed that his particular prodrug compound had some anti-cancer effects. (Tr. at 144:20-22.) While successful for Murdock's intended uses, a POSA in 1994 would not have viewed slow conversion more generally as a desirable property, since slow conversion could potentially cause the prodrug not to work at all, or to result in unwanted effects due to "polypharmacology." (Tr. at 291:6-13, 320:14-22, 465:2-466:1; 497:5-498:4.)

192. Neither *Anderson* et al. nor *Mosher* would have motivated a POSA in 1994 to make the specific compound fosaprepitant dimeglumine from compound 96. In particular, as explained above, these documents describe types of prodrugs that are very different from fosaprepitant dimeglumine, and which could not lead to that compound if applied to compound 96. (Tr. at 478:11-14, 478:24-479:9, 481:16-24.)

193. A POSA in 1994 would not have been motivated to specifically make the dimeglumine salt of the compound fosaprepitant. (Tr. at 494:15-497:4.)

194. A POSA in 1994 would have lacked specific data concerning compound 96, let alone the compound fosaprepitant (which itself was not in the prior art). Thus, there was no apparent justification in the prior art for specifically making a dimeglumine salt of fosaprepitant. (Tr. at 494:25-495:23.)

195. While Dr. Sherman testified about a generic disclosure of meglumine (among a list of other salts) in the context of the '889 application, a POSA in 1994 would have appreciated that the chemistry of compound 96 is not appropriate to form a salt with meglumine. (Tr. at 495:24-496:3.)

196. Nor would the '380 patent have motivated a POSA in 1994 to make the dimeglumine salt of the unknown compound fosaprepitant. A POSA would have understood that the phosphonate compounds described in the '380 patent are very unlike the structure of fosaprepitant (which has a phosphoryl group bonded to a triazolone nitrogen in a particular complex molecule). (Tr. at 496:4-497:4.)

197. In general, a POSA in 1994 would not have had any specific biological or pharmacokinetic data for compound 96. Therefore, a POSA in 1994 would not have reasonably expected to succeed in taking that relatively unknown compound and then adding a further layer of complexity by modifying it into a prodrug compound with different properties. (Tr. at 461:2-462:5; 465:13-466:5; PTX-016.0007-8.)

198. In contrast to a POSA in 1994, who had no specific biological or pharmacokinetic data on compound 96, the Merck researchers who succeeded in making and developing fosaprepitant dimeglumine had access to extensive confidential information regarding compound 96. (Tr. at 493:10-15.) For example, the Merck researchers had prepared a 300-page long RMC report on compound 96 (also known as L-754,030) as of December 1993 that contained substantial *in vitro* and *in vivo* data on that compound – none of which were available in the prior art. (Tr. at 484:18-485:6; see generally PTX-150.) This report itself followed a long history of experimental work synthesizing and testing compounds to understand their properties chemically and biologically. (Tr. at 655:20-656:3, 787:12-788:5.)

199. Without the benefit of any biological and pharmacokinetic data specific to the parent molecule, a POSA in 1994 would not have had any reasonable expectation that fosaprepitant dimeglumine – if it could even have been made – would have actually worked as a prodrug, i.e., remaining stable prior to administration but then converting at the appropriate time to an active

moeity in the body. (Tr. at 428:10-20, 463:12-18; PTX-016.0007; PTX-019.0001.) For example, if the resulting compound converted too slowly, it could have resulted in an ineffective drug or an undesirable situation of “polypharmacology.” (Tr. at 497:5-498:4.) And if the resulting compound converted too rapidly, it might result in clumps of the original insoluble parent molecule being recreated in the blood stream, which Dr. Sherman conceded would be undesirable. (Tr. at 498:5-12; see also Tr. at 89:19-21.)

200. For example, *Murdock* et al. demonstrated the unpredictability of the conversion rates of prodrugs. *Murdock* describes a prodrug that has two phosphoryl groups within the same compound – and yet the body treats these two groups differently, hydrolyzing one in approximately 12 minutes, but then taking several hours to cleave the other. (Tr. at 497:21-23; PTX-040.0002.)

201. *Mosher* further demonstrated the unpredictability of the conversion of prodrugs, because it describes an attempted prodrug that did not convert at all, and thus had no *in vivo* effect. (Tr. at 481:16-24; PTX-039.0002-3.)

202. Nor would a POSA have reasonably expected to be able to make fosaprepitant dimeglumine from compound 96, even in view of the alleged prior art such as the *Murdock* documents (PTX-040 and PTX-063). To the contrary, a POSA in 1994 could not have applied the chemistry of *Murdock* to compound 96 to produce fosaprepitant dimeglumine. (Tr. at 146:15-18.) Further, none of the other alleged art such as *Anderson* et al. or *Mosher* would have instructed a POSA on the chemistry needed to make fosaprepitant dimeglumine. (Tr. at 478:11-14, 478:24-479:9, 481:16-24.)

203. A POSA in 1994 also would not have had any reasonable expectation that the compound fosaprepitant dimeglumine – if it could be made – would have had sufficient stability

(e.g., on the shelf or in solution) to work as a useful prodrug. (Tr. at 463:12-18; PTX-016.0007; PTX-019.0001.)

204. For example, *Murdock* et al. demonstrates the complexity of stability issues, where the salt form of a bisphosphorylated prodrug is far less stable than its free acid, and where a monophosphoryl version of the prodrug is also far less stable than the bisphosphorylated prodrug. (Tr. at 474:1-18; PTX-040.0002.)

205. In the context of selecting compounds for modification, and further pursuing their modification, a POSA in 1994 would have considered the properties of such compounds. In particular, the properties of a compound would have served as the decision making checkpoints for a POSA at that time, and would have been integral to every step that the POSA might have taken in that context. (Tr. at 501:14-502:20.)

## **H. Secondary Considerations**

### **1. Unexpected Properties of Fosaprepitant Dimeglumine**

206. At trial, Dr. Roush explained that fosaprepitant dimeglumine has unexpected properties in its (1) stability prior to administration; (2) rapid conversion *in vivo* despite its excellent stability outside of the body; (3) exceptional solubility prior to administration; and (4) safety and efficacy *in vivo* compound. (Tr. at 498:25-501:9; PTX-303.)

207. Fosaprepitant dimeglumine is shelf-stable as a drug for up to 24 months before administration into the body. (Tr. at 499:3-8; PTX-213.0010.)

208. The stability of fosaprepitant dimeglumine could not have been predicted before it was synthesized and tested. (Tr. at 499:7-8.)

209. As Dr. Hale testified at trial, fosaprepitant dimeglumine is amorphous, meaning that it would not crystallize despite his and Dr. Dorn's best efforts to attempt crystallization. Even

though fosaprepitant dimeglumine does not crystallize, fosaprepitant dimeglumine unexpectedly remains stable in the solid form. (Tr. at 689:7-13, 693:10-17, 694:6-695:6; PTX-303.0012.)

210. Dr. Sherman described the uncertainty associated with amorphous compounds on direct examination, stating that, “in chemical compounds that are solid instead of liquid, the solid forms can be manipulated into certain structural forms; one of them is called amorphous form. And there’s no way to predict whether that type of work, which requires a lot of trial and error with no guarantee of success at all, that it would have helped.” (Tr. at 135:20-25.)

211. The unpredictability of stability was further demonstrated by the testimony of Dr. Mills, who explained that fosaprepitant as a dipotassium salt “decomposed very rapidly, and I recall thinking this was not suitable as a drug ever.” (Tr. at 798:4-10.) He continued, “[f]or a synthetic substance to be medicinally useful, you have to be able to have material that is chemically stable enough to be manufactured, processed, packaged, stored, shipped, distributed and made available to patients for a considerable period of time. The decomposition of the compound at that point in time was so rapid that I recall thinking that was not consistent with a medicine.” (Tr. at 798:12-22.)

212. Despite the fact that fosaprepitant dimeglumine is unexpectedly stable prior to administration, it is still able to function as a prodrug *in vivo*, breaking down within the body so rapidly that it is no longer detectable within 30 minutes after intravenous infusion in humans. (Tr. at 500:2-3; PTX-184.0002; PTX-023.0004.)

213. As Dr. Roush testified at trial, the rapid conversion of fosaprepitant dimeglumine *in vivo* is unexpected. (Tr. at 498:25-499:4, 500:2-3.) This is further confirmed by Sandoz’s reliance on *Murdock et al.* (1993) (PTX-040), which taught in contrast that the conversion of the prodrug

described in that article to its parent compound, bisantrene, required “several hours.” (Tr. at 145:13-16.)

214. Merck’s experimental data established that in aqueous solution, outside of the body, fosaprepitant dimeglumine is over 50,000 times more soluble than the compound now known as “aprepitant.” (Tr. at 500:18-24; PTX-150.0300; PTX-183.0003.) Such a large increase in solubility is unexpected. (Tr. at 500:18-24.)

215. As Dr. Sherman testified at trial, “[i]f a – clumps of solid material get into the blood stream that’s dangerous.” (Tr. at 89:19-21.) The fact that the fast converting fosaprepitant dimeglumine can rapidly revert *in vivo* following intravenous administration into a compound that is itself insoluble, yet safely provide antiemetic efficacy, is unexpected. (Tr. at 500:18-24.)

216. Further, fosaprepitant dimeglumine’s ability to provide three days of antiemetic therapy with a single 150 mg dose, even though it is rapidly converted into its parent compound within 30 minutes of administration, is unexpected. (See Tr. at 407:9-11; PTX-030.) At trial, Dr. Rogers explained that this “once and done” dose of 150 mg EMEND® for Injection provides “a tremendous advantage to requiring that they take oral medications” for three days. (Tr. at 398:22-399:5, 405:23-406:6, 409:14-21.)

## **2. The Claimed Compound Filled A Long Unfulfilled Need**

217. CINV is one of the most debilitating side-effects of chemotherapy. (Tr. at 392:24-393:18.) CINV can persist for days and causes retching. (*Id.*) During this period, patients lose a tremendous amount of body weight. (*Id.*) If they cannot maintain nutrition, they may become fatigued and depressed; and patients may have to be admitted to the hospital for intravenous fluid resuscitation. (*Id.*) Patients may find CINV so debilitating that they refuse chemotherapy to treat their cancer, even in situations where the outcome would likely have been better with

chemotherapy. (Tr. at 393:19-394:6.) CINV also impacts the lives of the family and friends around the patient who have to take time out to care for the patient debilitated by CINV. (Tr. at 392:24-393:18.)

218. Acute CINV occurs immediately and within approximately 24 hours after the administration of chemotherapy. (Tr. at 392:6-17.)

219. Delayed CINV can be described as the nausea and vomiting that occurs after the acute phase is over. (See Tr. at 392:6-23.)

220. There are several factors that place cancer patients at higher risk for CINV. (Tr. at 394:7-395:24.) The most important factor is the choice of chemotherapeutic agent. (*Id.*)

221. Patients treated with highly emetogenic chemotherapy agents, such as cisplatin, to aggressively treat cancers are almost always likely to experience CINV. (*Id.*)

222. Moderately emetogenic agents also increase the risk factor for CINV, although not to the same extent as highly emetogenic agents. (*Id.*)

223. Initially, in the 1970s, it was thought that the dopamine pathway, which acted on the brain, was involved in CINV. (Tr. at 396:12-397:11.) High dose metoclopramide, which blocked the dopamine pathway, was given to cancer patients undergoing chemotherapy to control CINV. (*Id.*) Metoclopramide was not approved by the FDA for preventing CINV, and this treatment was suppositional. (*Id.*) Metoclopramide also tended to make patients sick, requiring hospitalization, and additional drugs were prescribed to overcome the side-effects of metoclopramide. (*Id.*)

224. Subsequently, it was determined that a peripheral pathway affecting the gut called the serotonin pathway, which stimulated 5-HT<sub>3</sub> receptors, was involved in causing acute CINV. (Tr. at 397:12-24.)

225. Based on this understanding, the 5-HT<sub>3</sub> receptor antagonist class of drugs was developed in the 1990s to block the serotonin pathway. (*Id.*)

226. Delayed CINV, however, remained a troubling side-effect of chemotherapy. (Tr. at 397:25-398:11.)

227. As of 1994, there were no antiemetic NK-1 receptor antagonist drugs available for the treatment of patients undergoing cancer chemotherapy. (Tr. at 398:12-21.)

228. In 2003, the first NK-1 receptor antagonist, EMEND® Oral, was approved by the FDA to block the substance P / NK-1 receptor pathway. (Tr. at 398:12-21, 410:13-18.) The active ingredient in the EMEND® Oral drug product was aprepitant. (Tr. at 408:21-22, 876:2-5.)

229. EMEND® Oral provided an improvement in the management of CINV caused by highly emetogenic chemotherapy, but it required cancer patients to take a three-day regimen, consisting of 125 mg of aprepitant on day 1, and 80 mg each on days 2 and 3. (See Tr. at 398:12-21, 875:10-17.)

230. In 2008, the 115 mg EMEND® for Injection was first approved by the FDA. (Tr. at 398:12-21, 884:14-16.)

231. In 2010, the FDA approved 150 mg EMEND® for Injection. (Tr. at 398:20-24.)

232. The active ingredient in the EMEND® for Injection drug product is fosaprepitant dimeglumine. (Tr. at 400:10-15, 401:8-10, 912:5-12; PTX-303.0027.)

233. In the 21 years since 1994, when fosaprepitant dimeglumine was invented, it has been the only NK-1 receptor antagonist drug product approved by the FDA for intravenous administration. (Tr. at 909:24-910:3.)

234. The efficacy of the 150 mg single-dose EMEND® for Injection was demonstrated by a double-blind controlled clinical study of cancer patients randomized to receive either EMEND®

Oral or the 150 mg single-dose EMEND® for Injection, which is considered a gold standard study and has been published in the Journal of Oncology. (Tr. at 403:17-404:2, 404:13-18; PTX-30.)

235. The single dose of 150 mg EMEND® for Injection (fosaprepitant dimeglumine) is at least as effective as the three day 285 mg EMEND® Oral regimen. (Tr. at 407:9-11; PTX-030.)

236. For patients who are at risk of CINV caused by HEC, the ability to give a patient a one-time dose of EMEND® for Injection in the clinic provides a significant advantage over requiring the patient to take oral medications for two days following the clinic visit. (Tr. at 405:23-406:6, 409:14-21.)

237. To properly prevent highly emetogenic CINV, both the 5-HT3 pathway and the substance P / NK-1 pathway must be blocked. (Tr. at 399:21-400:5.) While the 5-HT3 receptor antagonists such as Zofran® blocks the 5-HT3 pathway, an NK-1 receptor antagonist such as EMEND® for Injection is necessary to block the other pathway to effectively control CINV caused by highly emetogenic chemotherapy. (Tr. at 399:21-400:9, 416:11-21.)

238. The combination therapy containing the 150 mg single-dose EMEND® for Injection, a corticosteroid and a 5-HT3 receptor antagonist used in combination for the prevention of acute and delayed CINV caused by HEC has been embraced by the medical community. (Tr. at 401:21-402:18.)

239. This acceptance by the medical community is indicated by the fact that MASCC, ASCO, and NCCN, which provide guidelines to health care professionals as to the best treatment practices based on a review of the clinical trials and available data, have independently recommended the 150 mg single-dose EMEND® for Injection in combination with a 5-HT3 and a corticosteroid for the prevention of acute and delayed CINV caused by HEC. (Tr. at 401:21-402:18, 910:4-20; PTX-017.0007; PTX076.0006-7; PTX-311.0006.)

240. The ASCO guidelines also state that fosaprepitant is “endorsed by the Committee as an acceptable NK-1 receptor antagonist.” (Tr. at 911:3-18; PTX-017.0008.)

### **3. The Commercial Success Of The Compound**

241. Dr. Sherman admitted during cross-examination that EMEND® for Injection (fosaprepitant dimeglumine) is an embodiment of the Asserted Claims of the ’336 patent. (Tr. at 182:21-183:5.) This testimony was consistent with the testimony of Dr. Roush. (Tr. at 423:6-424:2, 426:12-20.)

242. Because EMEND® for Injection embodies the features of the Asserted Claims of the ’336 patent, a nexus between those claims and the indicators of EMEND® for Injection’s commercial success, such as sales and the patented features of the claimed invention, is presumed. (Tr. at 600:6-14.)

243. EMEND® for Injection has achieved significant sales. (Tr. at 401:21-402:18, 580:12-581:3, 584:6-16.)

244. EMEND® for Injection has generated more than \$650 million in net sales from 2008, when it was introduced, through 2013. (Tr. at 580:12-581:3; PDX-403.)

245. Sales of EMEND® for Injection have increased steadily over time from its introduction in 2008 through 2013, reflecting increasing demand for EMEND® for Injection by health care professionals who are prescribing EMEND® for Injection, as Dr. Rogers’s testimony confirmed. (See Tr. at 405:3-406:6, 584:6-16; PDX-403.)

246. Sandoz’s commercial success expert, Ms. Lawton, agreed that EMEND® for Injection has generated significant revenue and significant profits for Merck, and would be deemed commercially successful from an ordinary business person’s standpoint. (Tr. at 922:17-923:1, 923:12-924:13.)

247. The combined sales of the EMEND® products also steadily increased over this time period. (Tr. at 584:20-585:21; PDX-404.) At trial, Mr. Sims testified that this growth in sales of the EMEND® products were driven by sales of EMEND® for Injection, because, as shown in PDX-404, although sales of EMEND® Oral started declining, sales of EMEND® for Injection were increasing at a significantly higher rate such that the sales of the two EMEND® products as a whole increased every year. (*Id.*)

248. In addition to significant sales and profits reflective of commercial success, the market share data for EMEND® for Injection provides further evidence of commercial success. (Tr. at 590:7-12.)

249. As Ms. Lawton confirmed, the relevant market for commercial success analysis is composed of products that have reasonable interchangeability for the purposes which they are produced. (Tr. at 919:23-920:9.) Ms. Lawton further confirmed that for products to be in the relevant market, they have to have the ability, either actual or potential, to take significant amounts of business from each other. (*Id.*)

250. Mr. Sims likewise testified that the relevant market for commercial success is the market containing the products that compete with EMEND® for Injection. (Tr. at 601:4-11.)

251. According to Ms. Lawton and Mr. Sims, EMEND® for Injection was a potential substitute for EMEND® Oral that competed for sales, while a 5-HT<sub>3</sub> receptor antagonist was not a substitute for EMEND® for Injection because they are prescribed together. (Tr. at 587:17-588:8, 601:4-11, 614:3-23, 920:14-21.) Ms. Lawton agreed that the 5-HT<sub>3</sub> receptor antagonist and corticosteroid (dexamethasone) offer a base level of protection and the NK-1 receptor antagonist is an adjunct that offers an additional level of protection. (Tr. at 910:21-24.)

252. EMEND® for Injection was a potential substitute of EMEND® Oral because according to Dr. Rogers, during the relevant period these were the only two FDA approved drugs in the NK-1 receptor antagonist class that could be used in the combination therapy along with a corticosteroid and a 5-HT3 receptor antagonist for the prevention of acute and delayed CINV caused by HEC. (See 398:12-400:9.)

253. The relevant market for the purpose of determining commercial success is the NK-1 receptor antagonist market, which contained EMEND® for Injection and EMEND® Oral. (Tr. at 602:12-16, 876:16-23, 920:17-21.)

254. When EMEND® for Injection was first launched in 2008, EMEND® Oral held a hundred percent of the NK-1 receptor antagonist drug market. (Tr. at 590:7-15.) Nevertheless, EMEND® for Injection went on to become the market leader with a market share exceeding 79 percent of the market in terms of both sales revenue and number of patient cycles as of 2013. (Tr. at 590:7-591:6.) Ms. Lawton agreed that EMEND® for Injection dominated the NK-1 receptor antagonist market. (Tr. at 928:23-929:5.)

255. Sandoz relies on certain internal Merck marketing department materials, which, in some instances, discussed a total antiemetic drug product market, including 5-HT3 receptor antagonists. (Tr. at 604:4-607:20, 866:22-867:4, 870:10-873:3; PTX-224.0010; PTX-225.0013; PTX-230.0059.) These marketing materials were not prepared for the purposes of analyzing the relevant market for commercial success of a patented product, and they do not show that the 5-HT3 receptor antagonists are interchangeable with EMEND® for Injection and are competing with it for sales.

256. Other internal Merck marketing materials describe the competition as being NK-1 receptor antagonists, and do not include 5-HT3 receptor antagonists. (Tr. at 613:24-615:19; PTX-

225.0003) During her direct examination, Ms. Lawton defined the total market based, in part, on her stated understanding that oncology healthcare guidelines for medical professionals recommend a three drug combination regimen including NK-1 receptor antagonists for moderately emetogenic chemotherapy. (Tr. at 868:19-869:16; 907:19-25.) This analysis of the market was inaccurate because the guidelines recommend only a two drug combination regimen for moderately emetogenic chemotherapy that does not include an NK-1 receptor antagonist. (Tr. at 908:5-20; PTX-017.0008.)

257. Nonetheless, even if one were to look at the broader antiemetic market argued for by Sandoz, EMEND® for Injection still has a significant market share, capturing more than 25 percent of the market by 2013. (Tr. at 607:21-608:3.)

258. Given the significant revenues and market share, EMEND® for Injection is a commercial success, and Ms. Lawton agreed that EMEND® for Injection is commercially successful from an ordinary business person's standpoint. (Tr. at 922:17-923:1, 923:12-924:13.)

259. As Mr. Sims testified, based on Dr. Rogers's un rebutted testimony about the clinical benefits of fosaprepitant dimeglumine, the commercial success of EMEND® for Injection is related to the properties of fosaprepitant dimeglumine. (Tr. at 405:3-406:6, 600:6-25.) Sandoz failed to prove that commercial success was due to factors unrelated to the properties of fosaprepitant dimeglumine. Ms. Lawton agreed that if the active ingredient fosaprepitant dimeglumine were extracted from EMEND® for Injection, the clinical efficacy of EMEND® for Injection would not be provided. (Tr. at 927:18-928:2.) Ms. Lawton also agreed that the demand for EMEND® for Injection is at least partly due to its active ingredient fosaprepitant dimeglumine. (Tr. at 928:3-6.)

260. Although Ms. Lawton testified that EMEND® for Injection is sold at a lower cost than EMEND® Oral, she admitted that she did not ascertain what the difference was in terms of the actual out-of-pocket cost to a patient between EMEND® for Injection and EMEND® Oral. (Tr. at 927:1-7, 930:8-14.) Sandoz also did not provide any evidence demonstrating how, if at all, the difference in prices impacted the sales and market share of EMEND® for Injection. (See Tr. at 895:23-897:16.)

261. EMEND® for Injection is priced higher per milligram than EMEND® Oral, but, because the properties of fosaprepitant dimeglumine allow a single 150 mg dose of EMEND® for Injection to be as effective as 285 mg of EMEND® Oral in three doses, the overall price of a treatment regimen is slightly lower than for EMEND® Oral. (Tr. at 407:9-11, 591:10-592:21, 926:21-25; PTX-030.0006.)

262. However, the price for a treatment regimen of EMEND® for Injection also includes attendant administrative costs associated with administering an intravenous injection, which, if taken into account, would make the total cost to the payer for EMEND® for Injection and EMEND® Oral regimens consistent. (Tr. at 592:22-593:2.) This was not taken into consideration in Sandoz's analysis. (See, e.g., Tr. at 889:9-22, 894:16-23, 895:23-896:6, 897:7-12, 930:10-14.)

263. Sandoz did not prove that the commercial success of EMEND® for Injection was attributable to its price and not the properties of fosaprepitant dimeglumine. (See, e.g., Tr. at 591:7-592:1.)

264. Sandoz relied on certain marketing documents from Merck that discuss a life cycle management strategy. (Tr. at 891:20-893:18; DTX-245.0010.) But these documents discuss overall growth of the combined EMEND® Oral and EMEND® Injection sales. (*Id.*) Ms. Lawton

admitted that she does not have the background to say why a health care professional would prescribe a particular medication for CINV. (Tr. at 908:21-24.)

265. Dr. Rogers's testimony confirmed that the demand for a pharmaceutical product such as EMEND® for Injection is driven by the need of patients who are undergoing chemotherapy and their medical professionals who prescribe the best treatment options for these patients. (See Tr. at 405:3-406:6, see also Tr. at 597:9-598:1.)

266. Sandoz did not prove that the commercial success of EMEND® for Injection was due to a lifecycle management strategy unrelated to the properties of fosaprepitant dimeglumine. (See, e.g., Tr. at 597:1-598:1.)

267. Sandoz argued that leveraging of EMEND® Oral's existing market position resulted in the commercial success of EMEND® for Injection (Tr. at 903:12-22), but failed to provide any evidence that the ability of EMEND® for Injection to garner a dominant share of the existing EMEND® Oral market was unrelated to the properties of fosaprepitant dimeglumine. (See, e.g., Tr. at 903:12-22.) Ms. Lawton agreed that she does not have the background to say why a health care professional would prescribe a particular medication for CINV, and, therefore, could not provide an opinion that health care professionals prescribed EMEND® for Injection because Merck leveraged its existing EMEND® Oral market position. (Tr. at 908:21-24.)

268. Although Sandoz argued that an increase in the sales force drove sales of EMEND® for Injection, Sandoz did not analyze or provide any evidence showing that the differential increase in sales versus EMEND® Oral was due to the alleged increase in the sales force. (Tr. at 926:13-20.) Further, as Ms. Lawton agreed, Merck's sales force did not promote EMEND® for Injection using hyperbole or unsubstantiated marketing claims. (Tr. at 925:23-926:4.) Rather, Merck promoted EMEND® for Injection addressing the properties of fosaprepitant dimeglumine, which

constitute features of the invention. Moreover, Sandoz did not provide any evidence to show that the sales force failed to market both EMEND® Oral and EMEND® for Injection. (See, e.g., Tr. at 901:8-14.)

269. The sales force is a means of communicating the benefits of the product and making health care professionals aware of the properties of the drug product and its benefits. (Tr. at 598:19-599:11.) Although an increase in sales force may have a short-term impact on revenues because more health care professionals become aware of a product and may decide to try it, over the course of the product being on the market, that short-term effect dissipates because health care professionals will not continue to prescribe a pharmaceutical product that is not effective for patients. (Tr. at 599:12-19.)

270. The alleged increase in Merck's EMEND® for Injection sales force did not cause the success of EMEND® for Injection unrelated to the properties of fosaprepitant dimeglumine. (Tr. at 598:19-599:11.)

271. Sandoz argued that the out-of-pocket costs for patients for the EMEND® for Injection regimen was cheaper than the out-of-pocket costs for the EMEND® Oral regimen, but did not provide any analysis or evidence of what the difference in costs were, and how this difference was responsible for driving the commercial success of EMEND® for Injection unrelated to the properties of fosaprepitant dimeglumine. (See, e.g., Tr. at 902:25-903:11.)

272. Both EMEND® Oral and EMEND® for Injection have reimbursement structures, like many drugs, allowing the products to be used by patients without being prohibitively expensive. (Tr. at 599:20-600:5.)

273. Reimbursement structures did not cause the commercial success of EMEND® for Injection unrelated to its properties. (*Id.*)

274. Sandoz argued that “favorable practice economics” drove sales of EMEND® for Injection, citing a Merck internal marketing document that stated in the second bullet point that a “potential for financial benefit to the practice,” but that document also stated in the first bullet point a clinical advantage of EMEND® for Injection being “improvement in compliance.” (Tr. at 898:24-901:4; DTX-221.0011.) Ms. Lawton did not provide an analysis of how much, if any, of the increase in sales of EMEND® for Injection was due to “favorable practice economics” unrelated to the properties of fosaprepitant dimeglumine.

275. At launch in 2008, marketing and promotional expenses for EMEND® for Injection as a percentage of sales and on an absolute basis was 22 percent. (Tr. at 595:13-596:22.) By 2013, this had decreased to about seven percent. (*Id.*) There was no evidence of a correlation between the marketing and promotion of EMEND® for Injection and its sales. Essentially, while marketing and promotional expenses decreased every year since its launch in 2008 through 2013, sales of EMEND® for Injection continued to increase every year during this period. (*Id.*)

276. Mr. Sims concluded that Merck’s expenses were not excessive for the market. (Tr. at 595:13-596:22.) In addition, Ms. Lawton testified that EMEND® for Injection is an ethical pharmaceutical product, and as such is sold based on substantiated marketing claims rather than through hyperbole. (Tr. at 925:23-926:4.)

277. Ms. Lawton also agreed that Merck’s profit plan for 2012 to 2016 was to drive the growth of single-dose EMEND® for Injection with “limited cannibalization of EMEND Oral.” (Tr. at 927:8-11.)

278. Further, even though EMEND® Oral and EMEND® for Injection are both owned by Merck, Merck was not able to control the sales of EMEND® for Injection because both products were on the market competing with each other for sales from 2008 through 2013. (Tr. at 601:12-

25.) Merck did not withdraw EMEND® Oral and, by having both products available, health care professionals could prescribe whichever product they believed was most effective for their patients. (*Id.*) EMEND® for Injection's ability to take away sales from its competitor EMEND® Oral, which itself was a successful product, supports the proposition that EMEND® for Injection was successful.

#### **4. Copying**

279. At least three generic drug companies are seeking to copy fosaprepitant dimeglumine: Sandoz; Accord Healthcare, Inc. USA; and Fresenius Kabi, USA LLC.

280. Sandoz seeks to copy fosaprepitant dimeglumine even though it has filed an ANDA seeking approval to sell aprepitant and may do so in April of 2015. In particular, on October 15, 2010, Sandoz stipulated to and consented to entry of judgment and injunction against it in *Merck & Co. Inc. v. Sandoz, Inc.*, Civil Action No. 09-00890 (MLC)(LHG) (D.N.J. 2010), which was a Hatch-Waxman patent infringement action brought by Merck against Sandoz in connection with the filing of Abbreviated New Drug Application No. 90-999 by Sandoz for generic aprepitant. (See Tr. at 918:24-919:9; *Merck & Co. Inc. v. Sandoz, Inc.*, Civil Action No. 09-00890, ECF No. 120 (D.N.J. 2010) (hereinafter "Consent Judgment").)

281. Under the terms of the Consent Judgment, Sandoz was enjoined until April 18, 2015 from marketing its generic product. (See Consent Judgment at 25.)

282. Despite the fact that Sandoz has the option to market generic aprepitant, Sandoz is still seeking to copy EMEND® for Injection to market a generic version of fosaprepitant dimeglumine. (Tr. at 918:15-17.)

283. As Ms. Lawton agreed, even with the possibility that a generic version of aprepitant may become available in the market as early as April 2015, Sandoz sees enough value for fosaprepitant dimeglumine to pursue that as a generic drug. (Tr. at 918:15-17, 919:16-22.)

284. Ms. Lawton agreed that Sandoz pursues products that it believes it can “make a profit at selling.” (Tr. at 918:18-23.) This was consistent with the testimony of Sandoz by its Rule 30(b)(6) witness, Dr. Nandi, who upon reviewing Sandoz’s profit and loss statement for fosaprepitant confirmed that “sales are pretty much totally positive” and that Sandoz “will make some money” if they pursued fosaprepitant. (Tr. at 826:8-16; PTX-279.0007.)

#### **IV. CONCLUSIONS OF LAW**

##### **A. Applicability of Lead Compound Analysis**

This case turns, primarily, on whether a lead compound analysis is necessary to Sandoz’s *prima facie* obviousness case, and, if so, whether the compound now known as aprepitant would have been the logical choice for modification to a person of ordinary skill in the art at the time that the compound now known as fosaprepitant dimeglumine was developed. Sandoz has relied largely on the case of *Pfizer v. Apotex*, 480 F.3d 1348 (Fed. Cir. 2007), in support of its argument that no lead compound analysis is necessary here. However, the *Pfizer* case is distinguishable from the circumstances here. In *Pfizer*, the Federal Circuit was faced with an appeal from a district court opinion that assumed a *prima facie* case of obviousness based upon the patent examiner’s initial rejection of the patent application for obviousness. The district court, therefore, never addressed any inquiry as to a lead compound because it presumed that the *prima facie* obviousness case was met. *Id.* at 1359. Further, it is unclear from the opinion whether such an argument was ever presented to the district court or the Federal Circuit on appeal. In other words, the circuit court did not perform a lead compound analysis because the parties never

disputed that amlodipine was the compound to be modified—they merely disputed whether it would have been obvious to create a besylate salt form of the compound based on the prior art. *Id.* at 1356-61. Here, however, there is a dispute as to which compound a POSA would have sought to modify. The ‘889 application, and the ‘699 patent, both claim 601 different morpholine compounds.

Sandoz has raised similar arguments as to the cases of *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013), and *Merck & Co., Inc. v. Biocraft Labs., Inc.*, 874 F.2d 804 (Fed. Cir. 1989). However, these arguments are likewise unavailing. In *Galderma*, the circuit court was faced with the appeal from a judgment holding that the claims of certain patents for an acne lotion treatment were valid. 737 F.3d at 734. The issue in that case was that the prior art disclosed that the effective concentration of the active ingredient, adapalene, in the acne medication could be anywhere from 0.1% to 1%, and the patented compound utilized a concentration of 0.3%. *Id.* at 734-35. It does not appear that the parties ever brought up lead compound analysis as an issue before the court in that matter.

Similarly, in *Biocraft Labs.*, the Federal Circuit reviewed the judgment of a district court that upheld the validity of a patent on a diuretic, the claimed compound of which was actually the combination of two diuretic agents disclosed in a prior patent. 874 F.2d at 805-807. The circuit court reversed the judgment of the district court, and invalidated the patent for obviousness, on the grounds that the prior patent literally encompassed the combination of the two diuretic agents in the patent under review, thus making the combination obvious. The Federal Circuit stated: “[t]he [prior] patent expressly teaches ‘that when co-administered with other diuretic agents known to enhance the elimination of potassium ions along with sodium ions, the novel pyrazinoylguanidines of this invention will reduce the excretion of potassium ions

and thus overcome this undesirable property of other diuretic agents.” *Id.* at 807. Therefore, the court concluded, “‘success’ is not dependent upon random variation of numerous parameters. On the contrary, the [prior] patent instructs the artisan that any of the 1200 disclosed combinations will produce a diuretic formulation with desirable sodium and potassium eliminating properties.” *Id.* Because the prior patent itself disclosed the *exact* combination used in the patent under review, as well as some data regarding the efficacy of the combination, the circuit court found that there was obviousness even in the absence of a lead compound analysis. *See id.* at 808.

Here, while it is true that aprepitant and “pharmaceutically acceptable salts” of aprepitant were disclosed in the ‘889 application, the patent at issue is for *fosaprepitant dimeglumine*—a pro-drug of the aprepitant salt. It is not the same compound previously disclosed by the ‘889 patent application. The purpose of the new chemical compound, fosaprepitant dimeglumine, is to increase the solubility of aprepitant in water, and separate *in vivo* into the active anti-emetic agent. (Tr. at 407:9-11, 423:9-15, 430:5-19, 433:1-8; PTX-030.) This is distinguishable from merely changing the dosage of a known combination of compounds, *Biocraft Labs.*, 874 F.2d at 808, or utilizing a known prior art dosage of an active ingredient in a medication, *Galderma Labs.*, 731 F.3d at 734. Therefore, this Court finds that it is necessary to perform a lead compound analysis in this case, and it will undertake that analysis as part of its inquiry into Sandoz’s *prima facie* case for obviousness.

### **1. Lead Compound Analysis and Prima Facie Obviousness**

As stated above, the appropriate factual inquiry in determining obviousness turns of the four *Graham* factors: “1) the scope and content of the prior art, 2) the level of ordinary skill in the art, 3) the differences between the claimed invention and the prior art, and 4) evidence of secondary factors, also known as objective indicia of non-obviousness.” *Eisai Co. Ltd.*, 533 F.3d at 1356

(citing *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)).

Because the third *Graham* factor is the most heavily contested here, the court will explore that first.<sup>14</sup>

**a. The Differences Between The Claimed Invention And The Prior Art**

The first step in determining “whether a new chemical compound would have been *prima facie* obvious over particular prior art compounds” is to “determine whether a chemist of ordinary skill would have selected the asserted prior art compound as [a] lead compound[], or starting point[], for further development efforts.” *Otsuka Pharmaceutical Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012). A lead compound analysis does not require the prior art to point to a single lead compound. *See Atlana Pharma AG*, 566 F.3d at 1008. Instead, if the prior art provides “a small and finite number of alternatives,” then this may support an inference of obviousness. *Eisai*, 533 F.3d at 1359. Nevertheless, “it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness.” *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007).

In deciding on which compounds a person of ordinary skill would select, the court “must look at the state of the [prior] art at the time the invention.” *Daiichi*, 619 F.3d at 1354. In other words, the court must not “fall[] prey to hindsight bias.” *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 403 (2007). In addition, “the analysis is guided by evidence of the compound’s pertinent properties.” *Otsuka*, 678 F.3d at 1292. That is, the selection of “a lead compound

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<sup>14</sup> The first two *Graham* factors—the scope and content of the prior art, and the level of ordinary skill in the art—are not heavily contested in this case. The parties have stipulated to much of this information. Therefore, the Court will focus on the third and fourth *Graham* factors in its analysis.

depends on more than just structural similarity, but also [on] knowledge in the art of the functional properties and limitations of the prior art compounds.” *Daiichi*, 619 F.3d at 1354. In short, “potent and promising activity in the prior art trumps mere structural relationships.” *Id.* The data that could Data that was considered as evidence of prior art compounds included the oral and intravenous activity of prior art compounds, their binding affinities, and the selectivity of the compounds. *Id.* at 1353-54.

At trial, Merck’s witnesses testified about the knowledge of prior art compounds that was available to a POSA in 1994. At that time, the NK-1 receptor antagonist art was still developing from the public’s perspective. (Tr. at 445:18-446:2.) The field began in the late 1980s with peptide compounds (small proteins), and turned in the early 1990s to non-peptide, small molecule antagonists. (Tr. at 440:1-5; PTX-314.0001; PTX-321.0012, 15.) There was significant interest in this field at that time from many major pharmaceutical companies. Trial showed that a POSA would have seen a “wall” of prior art that included well-studied, potent, and promising compounds from Pfizer, Sanofi, Glaxo, Rhone-Poulenc Rorer, and even Merck (none of which was the compound that later became aprepitant). (Tr. at 439:12-440:5, 815:24-816:8; *see generally* PTX-055; PTX-313; PTX-314; PTX-316; PTX-317; PTX-321; DTX-367; PDX-242; PDX-243.)

In addition, there were, disclosed in the ‘889 application, 601 different morpholine chemical compounds. Dr. Roush offered detailed testimony regarding the wall of NK-1 receptor antagonist prior art available to a POSA in 1994 separate and apart from the ‘889 compounds. He identified at least five other exemplary compounds—Pfizer’s CP-99,994, Rhone Poulenc’s RPR 100893, Sanofi’s SR140333, Glaxo’s Example 1 from EP ‘280, and *MacLeod’s* compound 7b—that, in stark contrast to compound 96, were well-characterized in the prior art, with specific

*in vitro* and *in vivo* data showing them to be highly potent, promising compounds, and even described as “leads for further optimization.” (Pl. Br. at 10.) Any of these NK-1 receptor antagonist compounds would have been a more reasoned starting point for modification for a POSA in 1994 than compound 96 – a compound among 601 named compounds in a patent application with no specific biological or pharmacokinetic data for any individual compound. (Pl. Br. at 10- 11; *see also Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1345 (Fed. Cir. 2000)).

Merck’s witnesses also testified about the confidential data that was available only to Merck scientists in 1994. Unlike the POSA, who had access only to the public disclosures of the prior art, several witnesses testified that Merck inventors had developed a wealth of confidential, non-public data regarding NK-1 receptor antagonists, including the Merck ’030 compound (which corresponds to compound 96). (Tr. at 493:10-15, 688:14-16; *see generally* PTX-150.) That compound 96 was of significant interest to the scientists at Merck in 1993 after experiencing problems with the ’694 compound has no bearing on whether a POSA in 1994 – without the benefit of Merck’s extensive confidential research – would have selected that compound from among the NK-1 receptor antagonist prior art as a starting point for further modification. *Otsuka*, 678 F.3d at 1296 (holding that “[t]he inventor’s own path” cannot be a basis for obviousness).

While Sandoz does not refute Merck’s contentions regarding available data on aprepitant, they contend that, in addition to the common practice of formulating prodrugs, the *Murdock* patent disclosed a synthetic scheme to convert triazolone functional groups into water soluble prodrugs for basic nitrogen atoms by phosphorylation makes the synthesis of fosaprepitant dimeglumine from aprepitant obvious.

Merck's response to this is that, in addition to other more common reactions in the prior art regarding prodrug synthesis, the triazolone functional group in aprepitant consists of acidic nitrogen atoms, as opposed to the basic nitrogen atoms modified in the synthetic scheme from *Murdock*. This would not lead a POSA to assume similar reactivity among the different molecules and therefore fail to motivate a POSA to utilize the *Murdock* reaction in modifying aprepitant and as such is Sandoz's transparent attempt to utilize hindsight. Although a POSA would be presented with only a few options in seeking to make an IV antiemetic, the lack of data on aprepitant renders it nonobvious. Similar to *Daiichi*, the present case presents a limited number of options with varying degrees of data available on each of the potential compounds. *Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 619 F.3d 1346 (Fed. Cir. 2010).

In the *Daiichi* case, the prior art presented five strong candidates: the '902 patent compounds, "L-158,809, DuP 532, the Eisai compounds, and valsartan." *Id.* at 1353. The Federal Circuit confirmed the district court's findings that "a medicinal chemist of ordinary skill would not have been motivated to select the '902 compounds over [the other compounds]." Crucial to this reasoning was the fact that the other compounds "all had been more thoroughly studied than the '902 ARBs." *See id.* While the prior art *did* include data on the '902 compounds' oral activity, it lacked data as to other properties of the compound. *Id.* This was vital to the court's reasoning, considering that the prior art "included not only data on oral activity for all but the Eisai compounds, but also data on the binding affinity and intravenous activity for [the other compounds]." *Id.* 1353-54.

Similar to the '902 compounds at issue in *Daiichi*, aprepitant represents one of only a handful of alternative compounds. *See id.* at 1353. However, a POSA at the relevant time would have only the information disclosed through the '889 application. This amounts to even less than

was available as to the ‘902 compounds. *Id.* In other words, a POSA would be presented with a similar decision as that in *Daiichi*, whether to proceed with a known compound that lacked data as to its properties, or to proceed with other compounds for which data was available. As in *Daiichi*, the lack of pharmaceutical data available on the compound in question renders aprepitant non-obvious in light of the available data on other compounds.

Furthermore, *Daiichi* made clear that the structural similarities between the proposed lead compound and the compound at issue are non-decisive. *See Daiichi*, 619 F.3d at 1354. “Proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of functional properties and limitations of the prior art compounds.” *Id.* Thus, the similarities between the structure of aprepitant and fosaprepitant dimeglumine are outweighed by the lack of pharmaceutical data available as to aprepitant’s chemical properties. To conclude that a POSA would have selected aprepitant, as opposed to other antiemetic compounds available, to modify, on the basis that *any* antiemetic should be turned into an IV would be to succumb to hindsight and circumvent the entire purpose behind lead compound analysis.

Finally, Dr. Sherman testified that the relatively short amount of time it took Merck to synthesize fosaprepitant (approximately three months) weighed in favor of the obviousness of the product. (*See, e.g.*, Tr. 136:4-15; 158:1-159:25.) However, this is a legally insufficient basis for the Court to find that fosaprepitant was an obvious chemical to be synthesized. *Otsuka*, 678 F.3d at 1296 (dismissing the argument that the short time to develop a drug was relevant to the finding of obviousness, and calling reliance on the inventor’s own path “hindsight”).

Because Sandoz has failed to establish that a POSA would have had sufficient motivation to select compound 96 as a lead compound for modification, Sandoz has not established a *prima facie* case of obviousness as to the Asserted Claims in the ‘336 patent.

### **B. Secondary Considerations**

Merck and Sandoz also presented evidence as to the fourth *Graham* factor—certain secondary considerations surrounding the alleged invalidity of the ‘336 patent for obviousness. “Objective indicia of non-obviousness include: (1) unexpected results; (2) commercial success; (3) long felt, unmet need; (4) copying; and (5) industry praise and recognition for the inventions.” *Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359, 381 (D.N.J. 2009) (internal citations omitted). Such considerations may “extend beyond what was known at the time of the invention and may include later discovered unexpected properties of the invention.” *Id.* (citing *Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004)).

Secondary considerations are often relied upon by courts as a part of the “totality of the evidence” presented with respect to obviousness. *Id.* (citing *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997)). While secondary considerations may “represent the most probative and cogent evidence in the record,” they are not considered to be controlling as to the court’s ultimate conclusion on obviousness. *Id.* at 382 (quoting and citing *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983) and *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988)).

Although this Court finds that Sandoz has not established a *prima facie* case of obviousness due to the lead compound analysis, assuming it had, the evidence regarding secondary considerations presented at trial further militate against a finding of obviousness. In

particular, the Court finds that the objective evidence of unexpected results, commercial success, fulfillment of a long-felt, unmet need, and copying are established by the evidence adduced at trial.

### **1. Unexpected Results**

“Evidence of ‘unexpected results’ allows a patent-holder to rebut a *prima facie* case of obviousness by showing that the ‘claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected.’” *Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d at 382 (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995)). The reason for this consideration finds its basis in a common sense principle: “that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious.” *Daiichi*, 670 F. Supp. 2d at 382 (internal citations and quotations omitted). In order for the claimed properties to be found “unexpected,” they “must be different in ‘kind and not merely in degree’ from the results of the prior art.” *Id.* (quoting *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996)). In addition, the unexpected claimed properties must be unexpected as compared with the closest prior art. *Daiichi*, 670 F. Supp. 2d at 382.

As stated above, at trial, Dr. Roush explained that fosaprepitant dimeglumine has unexpected properties in its (1) stability prior to administration; (2) rapid conversion *in vivo* despite its excellent stability outside of the body; (3) exceptional solubility prior to administration; and (4) safety and efficacy *in vivo* compound. (Tr. at 498:25-501:9; PTX-303.) Of particular importance to the Court are the last three unexpected properties—its rapid conversion *in vivo* to the parent compound; solubility; and safety and efficacy. *Murdock et al.* taught that a prodrug would not rapidly convert *in vivo* into its parent compound, instead requiring “several hours.” (Tr. at 145:13-

16.) That fosaprepitant dimeglumine converts within minutes is unexpected based upon the prior art.

As to solubility, in aqueous solution, outside of the body, fosaprepitant dimeglumine is over 50,000 times more soluble than aprepitant. (Tr. at 500:18-24; PTX-150.0300; PTX-183.0003.) Such a large increase in solubility is unexpected. (Tr. at 500:18-24.) In addition, the fact that the fast converting fosaprepitant dimeglumine is able to rapidly convert *in vivo* into what was previously an insoluble parent compound, yet remain soluble and provide three days of safe antiemetic efficacy in one dose, is unexpected when compared to the closest prior art, aprepitant. (Tr. at 407:9-11; 500:18-24.)

These unexpected results weigh in favor of a finding that the Asserted Claims are not invalid for obviousness.

## **2. Long-Felt, Unmet Need**

In addition to the unexpected results, fosaprepitant dimeglumine has fulfilled a long-felt, unmet need in the prevention of CINV. “[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem.” *Tex. Instruments, Inc. v. U.S. ITC*, 988 F.2d 1165, 1178 (Fed. Cir. 1993). In practical terms, courts “look to the filing date of the challenged invention to assess the presence of a long-felt and unmet need.” *P&G v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009). Here, Dr. Rogers testified that fosaprepitant dimeglumine was a great advance in the treatment and prevention of CINV because it could be administered intravenously in one dose which lasts for three days, and because it worked along the Substance P-NK-1 pathway, as opposed to the 5-HT3 pathway. (Tr. 395:25-399:20.) Dr. Rogers’ testimony on this matter was unrebutted and credible. This factor weighs in favor of a finding of nonobviousness.

### 3. Commercial Success

In addition to these factors, as stated above, the commercial embodiment of the claimed compound, fosaprepitant dimeglumine, has been a commercial success. “Commercial success is usually shown by significant sales in a relevant market.” *Daiichi*, 670 F. Supp. 2d at 384 (internal citations and quotation marks omitted). In order for sales to be considered significant, they “must be due to the claimed features of the invention, rather than factors such as advertising, superior workmanship, or other features within the commercialized technology.” *Id.*

EMEND® for Injection, which is the commercial embodiment of fosaprepitant dimeglumine, has achieved significant sales, generating more than \$650 million in net sales between 2008 and 2013. (Tr. at 401:21-402:18, 580:12-581:3, 584:6-16; PDX-403.) Sales of EMEND® for Injection have increased steadily between 2008 and 2013, which, according to Dr. Rogers, reflects an increasing demand for EMEND® for Injection by health care professionals who are prescribing EMEND® for Injection. (See Tr. at 405:3-406:6, 584:6-16; PDX-403.) Mr. Sims, Merck’s expert, testified that in the relevant market for EMEND® for Injection—the NK-1 receptor antagonist market—the product had a large and successful market share. (Tr. at 590:7-591:6, 602:12-16.) Although she ultimately came to a different conclusion as to the commercial success of EMEND® for Injection, even Sandoz’s expert, Ms. Lawton, agreed that EMEND® for Injection has generated significant revenue and significant profits for Merck, and would be deemed commercially successful from an ordinary business person’s standpoint. (Tr. at 922:17-923:1, 923:12-924:13.)

Therefore, the Court finds that the testimony regarding this factor weighs in favor of a finding of nonobviousness.

#### 4. Copying

Finally, others have sought to copy fosaprepitant dimeglumine. “Copying the claimed invention, rather than one in the public domain, is indicative of unobviousness.” *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 991 (Fed. Cir. 1988) (internal citations and quotation marks omitted). Here, although Sandoz is able to market generic aprepitant due to the expiration of the patent, it is nevertheless attempting to manufacture and market a generic fosaprepitant dimeglumine. (Merck Supp. Finding of Fact, ¶¶ 98-100.) Sandoz’s own expert, Ms. Lawton, noted that Sandoz pursues products that it can “make a profit at selling” (Tr. at 918:18-23). Ms. Lawton additionally testified that, despite its ability to market generic aprepitant, Sandoz sees enough value for fosaprepitant dimeglumine to pursue that as a generic drug. (Tr. 919:16-22.) Therefore, this weighs in favor of a finding of nonobviousness.

#### V. CONCLUSION

Sandoz has failed to present evidence of *prima facie* obviousness of the Asserted Claims of the ‘336 patent. Secondary considerations such as commercial success, copying, meeting a long-felt, unmet need, and unexpected results, also all weigh in favor of the non-obviousness of the Asserted Claims of the ‘336 patent. As a result, this Court finds that the Asserted Claims of the ‘336 patent are valid and enforceable. In addition, Sandoz stipulated that its proposed invention would infringe upon the Asserted Claims of the ‘336 patent in the event that it was ruled valid. Therefore, this Court finds that, if Sandoz were to launch its generic of fosaprepitant dimeglumine, it would infringe upon the Asserted Claims of the ‘336 patent. Judgment is therefore rendered in favor of Merck and against Sandoz on the issues of obviousness and infringement.

Dated: August 27, 2015

s/ Peter G. Sheridan  
PETER G. SHERIDAN, U.S.D.J.